B5

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 471/10, A61K 31/445, C07D 405/06, 405/14, C07K 5/06 — A1

(11) International Publication Number: WO 98/16527

(43) International Publication Date: 23 April 1998 (23.04.98)

(21) International Application Number: PCT/JP97/03704

(22) International Filing Date: 15 October 1997 (15.10.97)

(30) Priority Data:

PO 2988	15 October 1996 (15.10.96)	AU
PO 6764	14 May 1997 (14.05.97)	AU
PO 8753	25 August 1997 (25.08.97)	AU

(71) Applicant *(for all designated States except US)*: FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: TANIGUCHI, Kiyoshi [JP/JP]; 2-1-28, Minamiochiai, Suma-ku, Kobe-shi, Hyogo 654-01 (JP). KURODA, Satoru [JP/JP]; 3-6-21-207, Kotobuki-cho, Takatsuki-shi, Osaka 569 (JP). TSUBAKI, Kazunori [JP/JP]; 1-4-189, Oriidai, Uji-shi, Kyoto 611 (JP). SHIMIZU, Yasuyo [JP/JP]; 3-9-10, Motomachi, Naniwa-ku, Osaka-shi, Osaka 556 (JP). TAKASUGI, Hisashi [JP/JP]; 3-116-10, Mozu Umekita, Sakai-shi, Osaka 591 (JP).

(74) Agent: YOSHIKAWA, Toshio; Murahama Building 6F, 9-19, Higashinoda-cho 4-chome, Miyakojima-ku, Osaka-shi, Osaka 534 (JP).

(81) Designated States: AU, CA, CN, HU, IL, JP, KR, US, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

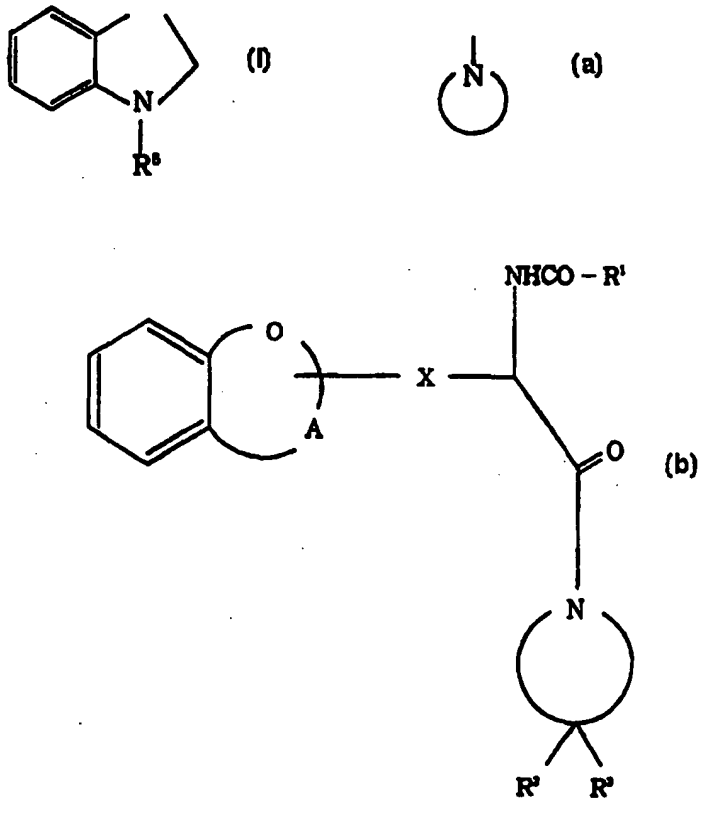
Published

With international search report.

(54) Title: BENZOXEPINE DERIVATIVES WHICH PROMOTE RELEASE OF GROWTH HORMONE

(57) Abstract

A pharmaceutically useful benzoxepine compound of formula (I), wherein R^1 is 3-azetidinyl, 4-piperidyl or a group of the formula: $-Y-NHR^4$, in which R^4 is hydrogen or amino protective group, and Y is lower alkylene or cyclo(lower) alkylene; R^2 is cyano and R^3 is aryl; R^2 is esterified carboxy and R^3 is ar(lower)alkyl: or R^2 and R^3 are linked together to form formula (a), in which R^5 is acyl, A is $-(CH_2)_n-$, in which n is 2, 3 or 4, vinylene or butenylene, X is bond or lower alkylene, and formula (b) is piperidino, and pharmaceutically acceptable salts thereof. The compound or a pharmaceutically acceptable salt thereof of the present invention has excellent promotion activity of growth hormone release for animals and human bodies.



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

DESCRIPTION

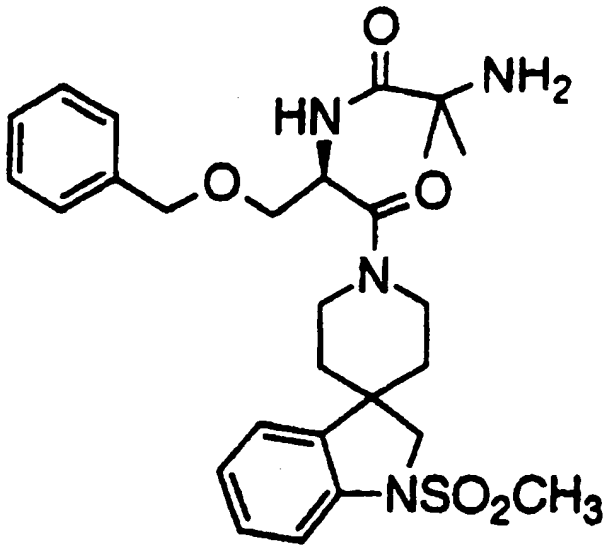
BENZOXEPINE DERIVATIVES WHICH PROMOTE RELEASE OF GROWTH HORMONE

TECHNICAL FIELD

The present invention relates to novel derivatives and pharmaceutically acceptable salts thereof.

BACKGROUND ART

With regard to the states of the arts in this field, for example, the following compound is known.



WO94/13696

DISCLOSURE OF INVENTION

The present invention relates to novel derivatives. More particularly, it relates to novel derivatives and pharmaceutically acceptable salts thereof which have pharmacological activities such as promotion activity of growth

hormone release, to processes for preparation thereof, to pharmaceutical composition comprising the same, and to a use of the same as a medicament.

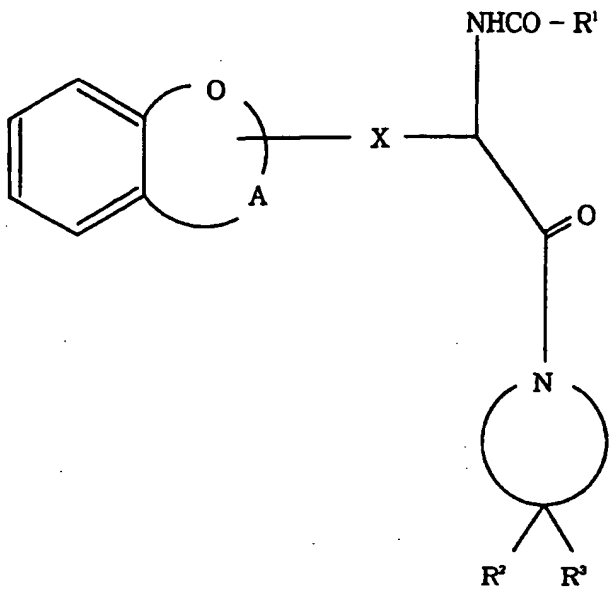
Accordingly, one object of the present invention is to provide the useful novel derivatives and pharmaceutically acceptable salts thereof which have pharmacological activities such as a promotion activity of growth hormone release, and the like.

Another object of the present invention is to provide processes for the preparation of said novel derivatives and pharmaceutically acceptable salts thereof.

A further object of the present invention is to provide a pharmaceutical composition comprising, as an active ingredient, said novel derivatives or a pharmaceutically acceptable salt thereof.

Still further object of this invention is to provide a use of said novel derivatives or a pharmaceutically acceptable salt thereof as a medicament which promotes activity of growth hormone release for animals and human bodies and they are useful for treatment of obesity in combination with an $\alpha 2$ or $\beta 3$ adrenergic agonist, osteoporosis in combination with parathyroid hormone, the catabolic effects of nitrogen wasting in combination with insulin-like growth factor 1, growth retardation, renal failure or insufficiency, schizophrenia, sleep disorder, skeletal dysplasia, depression, Alzheimer's disease, pulmonary dysfunction, hyperinsulinemia, ulcer, arthritis, cardiac dysfunction, replacement for elderly people, ALS, growth hormone deficient adults, physiological short stature including growth hormone deficient children , Turner's syndrome, intrauterine growth refardation, cachexia and protein loss due to cancer or AIDS and is also useful for stimulating the immune system, accelerating wound healing or bone fracture repair, improvement in muscle strength, and the like.

The object compounds of the present invention can be represented by the following general formula(I):

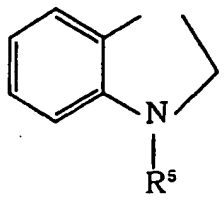


(I)

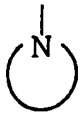
wherein R^1 is 3-azetidinyl, 4-piperidyl or
a group of the formula:

$$-Y-NHR^4$$

in which R^4 is hydrogen or amino protective group, and Y is lower alkylene or cyclo(lower) alkylene,
R^2 is cyano and R^3 is aryl;
R^2 is esterified carboxy and R^3 is ar(lower)alkyl: or
R^2 and R^3 are linked together to form



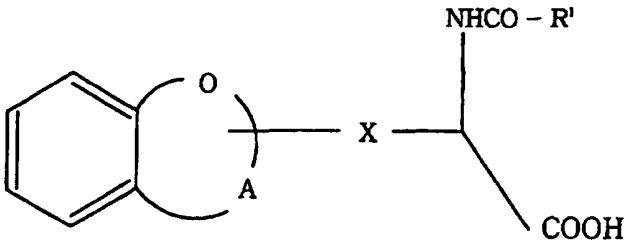
in which R^5 is acyl,
A is $-(CH_2)_n-$, in which n is 2, 3 or 4, vinylene or butenylene,
X is bond or lower alkylene, and



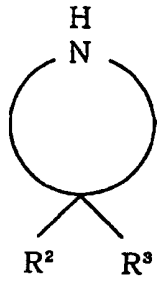
is piperidino.

According to the present invention, the novel derivatives of the object compounds (I) can be prepared by the following processes.

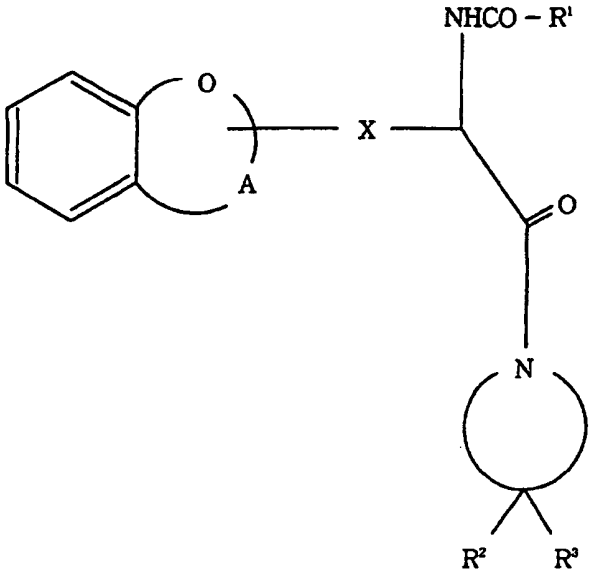
Process 1



(II)
or its reactive derivatives at the carboxy group or a salt thereof

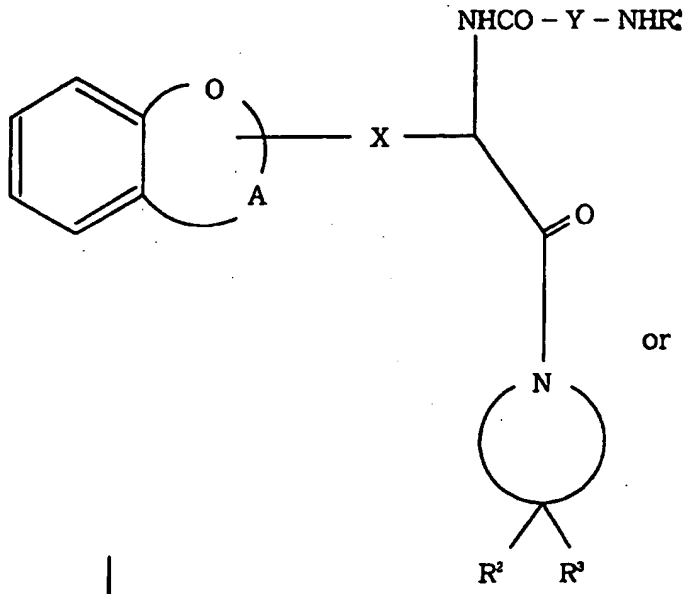


(III)
or its reactive derivatives at the amino group or a salt thereof



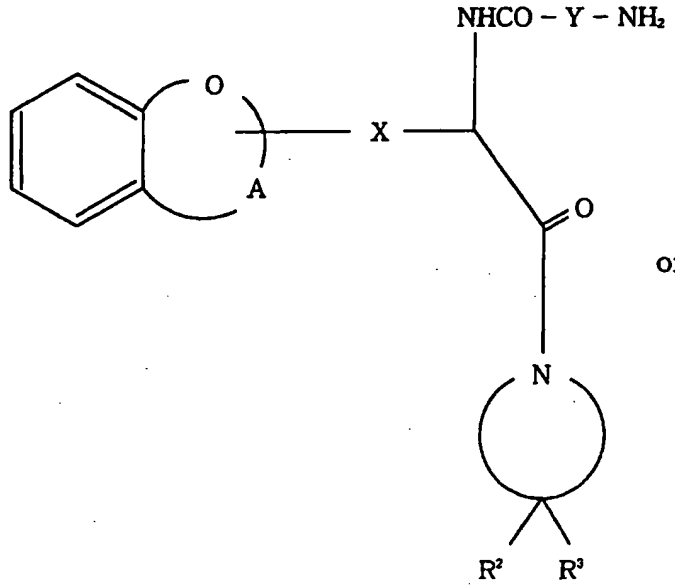
(I)
or a salt thereof

Process 2



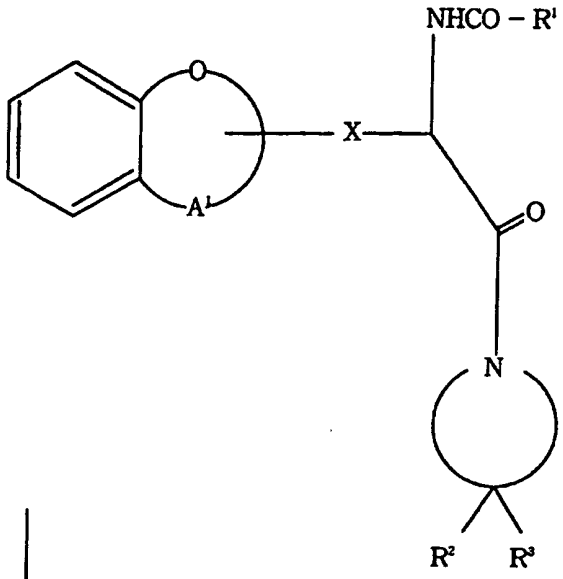
(I a)
or a salt thereof

removal of amino protective group



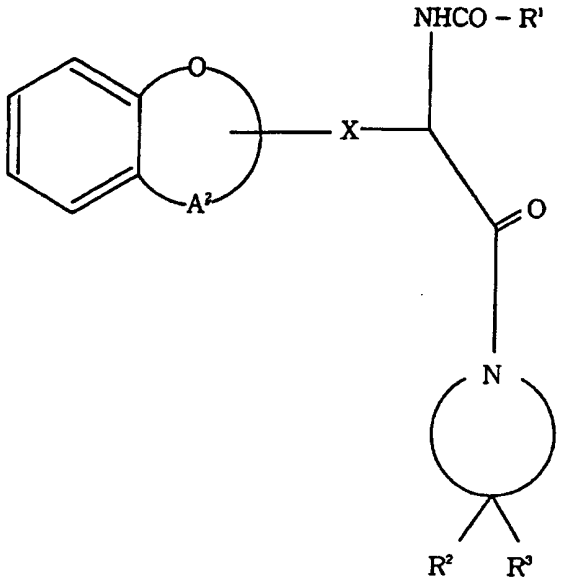
(I b)
or a salt thereof

Process 3



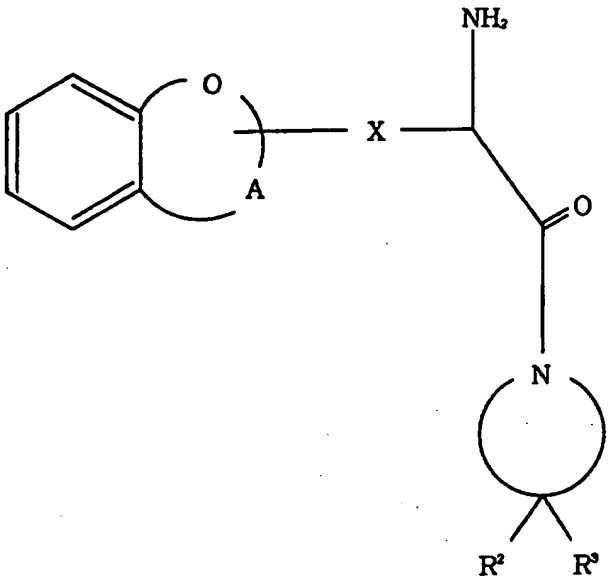
(I c)
or a salt thereof

reduction reaction

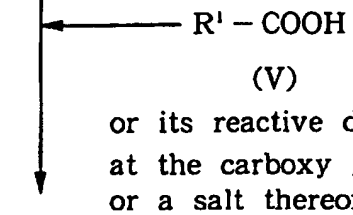


(I d)
or a salt thereof

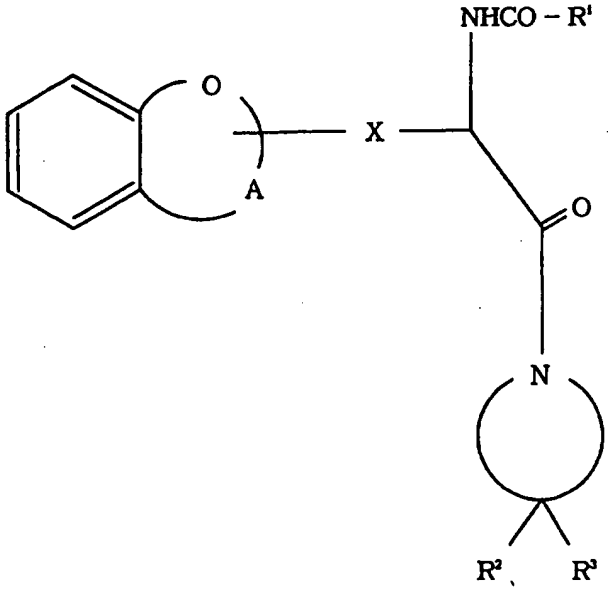
Process 4



(I V)
or its reactive derivatives
at the amino group
or a salt thereof



(V)
or its reactive derivatives
at the carboxy group
or a salt thereof



(I)
or a salt thereof

wherein R^1, R^2, R^3, A, X and Y are each as

defined above,

R_a^4 is amino protective group,

A^1 is vinylene or butenylene, and

A^2 is ethylene or tetramethylene.

Pharmaceutically acceptable salts of the object compounds (I) are conventional non-toxic salts and may include an acid addition salt such as an inorganic acid addition salt [e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.], an organic acid addition salt [e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.]; a salt with an amino acid [e.g. aspartic acid salt, glutamic acid salt, etc.]; and the like.

It is to be noted that each of the object compound (I) may include one or more stereoisomer such as optical isomer(s) and geometrical isomer(s) due to asymmetric carbon atom(s) and double bond(s) and all such isomers and mixture thereof are included within the scope of this invention.

The starting compound (II) and (IV) or a salt thereof can be prepared by the procedures described in the Preparations mentioned later or by a conventional method.

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions to be included within the scope of the invention are explained in detail as follows.

The term "lower" is intended to mean 1 to 6 carbon atom(s), preferably 1 to 4 carbon atom(s), unless otherwise indicated.

"Amino protective group" may include acyl such as lower alkanoyl [e.g. formyl, acetyl, propionyl, pivaloyl, hexanoyl, etc.], mono(or di or tri)halo (lower)alkanoyl [e.g. chloroacetyl, bromoacetyl, dichloroacetyl, trifluoroacetyl, etc.], lower alkoxycarbonyl [e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, t-butoxycarbonyl, t-pentyloxycarbonyl, hexyloxycarbonyl, etc.],

carbamoyl, aroyl [e.g. benzoyl, toluoyl, naphthoyl, etc.], ar(lower)alkanoyl [e.g. phenylacetyl, phenylpropionyl, etc.], aryloxycarbonyl [e.g. phenoxycarbonyl, naphthyloxycarbonyl, etc.], aryloxy(lower)alkanoyl [e.g. phenoxyacetyl, phenoxypropionyl, etc.], arylglyoxyloyl [e.g. phenylglyoxyloyl, naphthylglyoxyloyl, etc.], ar(lower)alkoxycarbonyl which may have suitable substituent(s) [e.g. benzyloxycarbonyl, phenethyloxycarbonyl, p-nitrobenzyloxycarbonyl, etc.]; ar(lower)alkyl such as ar(lower)alkylidene which may have substituent(s) [e.g. benzylidene, hydroxybenzylidene, etc.], mono(or di or tri)phenyl(lower)alkyl [e.g. benzyl, phenethyl, benzhydryl, trityl, etc.]; and the like.

Suitable "acyl" may include carbamoyl, aliphatic acyl and acyl group containing an aromatic ring, which is referred to as aromatic acyl, or an heterocyclic ring, which is referred to as heterocyclic acyl.

This acyl group may be derived, for example, from an organic carboxylic acid, an organic carbonic acid, an organic sulfuric acid, an organic sulfonic acid and an organic carbamic acid.

Suitable example of said acyl may be illustrated as follows:

Carbamoyl;

Aliphatic acyl such as lower or higher alkanoyl [e.g. formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridacanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl, icosanoyl, etc.]; lower or higher cycloalkylcarbonyl [e.g. cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, etc.]; lower or higher alkanesulfonyl [e.g. methanesulfonyl, ethanesulfonyl, etc.]; lower or higher alkoxysulfonyl [e.g. methoxysulfonyl, ethoxysulfonyl, etc.];or the like;

Aromatic acyl such as aroyl [e.g. benzoyl, toluoyl, naphthoyl, etc.]; ar(lower)alkanoyl [e.g. phenyl(lower)alkanoyl , etc.] or the like.

The acyl moiety as stated above may have 1 to 5, same or different, suitablesubstituent(s) such as halogen [e.g. fluorine, chlorine, bromine or iodine], lower alkyl [e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl, etc.], lower alkoxy [e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, pentyloxy, hexyloxy, etc.], hydroxy, carboxy, protected hydroxy, protected carboxy, mono(or di or tri)halo(lower)alkyl, N,N-di(lower)alkylamino [e.g. N,N-dimethyamino, N,N-diethylamino, N,N-dipropylamino, N,N-dibutylamino, N,N-dipentylamino, N,N-dihexylamino, N-methyl-N-butylamino, etc.], or the like.

Suitable "aryl" may include phenyl , tolyl, xylyl, mesityl, cumenyl, naphtyl, and the like, in which the preferred one is C_6-C_{10} aryl and the most preferred one is phenyl.

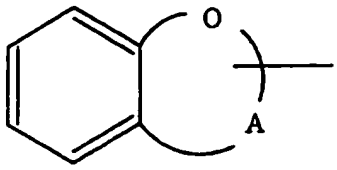
Suitable example of the ester moiety of an esterified carboxy may be the ones such as lower alkyl ester(e.g. methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, tert-butyl ester, pentyl ester, hexyl ester, 1--cyclopropylethyl ester, etc.)

Suitable "ar(lower)alkyl" may include trityl, benzhydryl, benzyl, phenythyl, and the like.

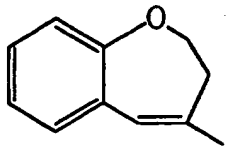
Suitable "lower alkylene" may include straight or branched one having 1 to 6 carbon atom(s), such as methylene, ethylene, propylene, trimethylene, tetramethylene, pentamethylene and hexamethylene, methyltrimethylene, dimethylmethylene.

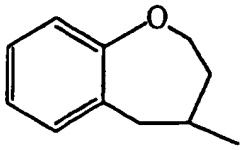
Suitable "cyclo(lower) alkylene" may include cyclopropylene , cyclopentylene and cyclohexylene.

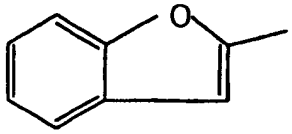
The preferred embodiments of the object compounds are as follows.



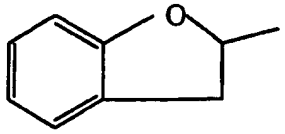
is the following formula :

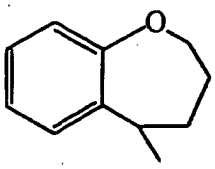


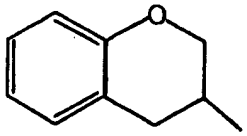
,


,


,



,


and


;

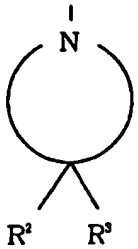
R^1 is 3-azetidinyl, 4-piperidyl or a group of the formula :

$$-Y-NHR^4$$

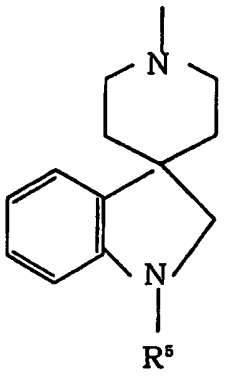
in which R^4 is hydrogen or acyl (e.g. lower alkoxycarbonyl, etc.), and

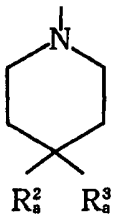
Y is lower alkylene or cyclo (lower) alkylene ;

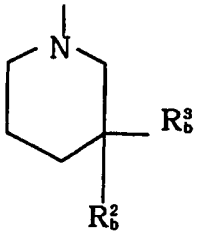
X is bond or lower alkylene ; and



is the following formula :







in which R^5 is acyl (e.g. lower alkanesulfonyl, etc.),

R^2_a is cyano,

R^3_a is aryl (e.g. phenyl, etc.),

R^2_b is esterified carboxy (e.g. lower alkoxycarbonyl, etc.),

R^3_b is ar (lower) alkyl (e.g. benzyl, etc.).

The processes for preparing the object compounds (I) are explained in detail in the following.

Process 1

The object compound (I) or a salt thereof can be prepared by reacting the compound (II) or its reactive derivatives at the carboxy group or a salt thereof with the compound (III) or its reactive derivatives at the amino group or a salt thereof.

The starting compound (II) or a salt thereof are novel and can be prepared by the manners of Preparations mentioned below or a similar manner thereto.

Suitable reactive derivative at the carboxy group of the compound (II) may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like. Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride within acid such as substituted phosphoric acid [e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.], dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, alkylcarbonic acid, (lower)alkanesulfonic acid [e.g. methanesulfonic acid, etc.], aliphatic carboxylic acid [e.g. acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.] or aromatic carboxylic acid [e.g. benzoic acid, etc.]; a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; or an activated ester [e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl [$(CH_3)_2N^+$=CH-] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, pentafluorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.], or an ester with a N-hydroxy compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc.], and the like. These reactive derivatives can optionally be

selected from them according to the kind of the compound (II) to be used.

Suitable salts of the compound (II) and its reactive derivative may be a base salt such as an alkali metal salt [e.g. sodium salt, pottasium salt, etc.], an alkaline earth metal salt [e.g. calcium salt, magnesium salt, etc.], an ammonium salt, an organic base salt [e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.], or the like, and an acid addition salt as exemplified for the compound (I).

Suitable reactive derivative at the amino group of the compound (III) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (III) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (III) with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethyl-syliy)acetamide, bis(trimethylsilyl)urea or the like; a derivative formed by reaction of the compound (III) with phosphorus trichloride or phosgene, and the like.

Suitable salts of the compound (III) and its reactive derivative can be referred to the ones as exemplified for the compound (I).

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction, These conventional solvent may also be used in a mixture with water.

In this reaction, when the compound (II) is used in a free acid form or its salt form, the reaction is preferably carried out in the presence of a conventional condensing agent such as carbodiimide or a salt thereof [e.g. N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-di-ethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-di-methylaminopropyl)carbodi-imide or hydrochloride thereof], N,N'-carbonylbis-(2-methylimidazole); diphenyl phosphorylazide, diethyl phosphorocyanidate, bis (2-oxo-3-oxazolidinyl) phosphinic chloride, etc.; N,N'-carbonyldiimidazole, N,N'-carbonylbis-(2-

methylimidazole);keteneimine compounds [e.g. pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine, etc.]; ethoxyacetylene; 1-alkoxy-1-chloroethylen; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; diphenyl phosphorylazide; thionyl chloride; oxalyl chloride; lower alkyl haloformate {e.g. ethyl chloroformate, isopropyl chloroformate, etc.}; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; benzotriazol-1-yl-oxy-tris-(dimethylamino)phosphoniumhexafluorophosphate; 1-hydroxybenzotriazole, 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride, etc.; or the like.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling, at ambient temperature or under warming.

Process 2

The compound (Ib) or a salt thereof can be prepared by subjecting a compound (Ia) or a salt thereof to removal reaction of the amino-protective group in R_3^4.

The starting compound (Ia) or a salts thereof are prepared by the process 1.

Suitable salts of the compounds (Ia) and (Ib) can be referred to the ones as exemplified for the compound (I).

This reaction is carried out in accordance with a conventional manner such as hydrolysis, reduction or the like.

The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid.

Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g. sodium, potassium, etc.]. an alkaline earth metal [e.g.

magnesium, calcium, etc.], the hydroxide or carbonate or bicarbonate thereof, hydrazine, trialkylamine [e.g. trimethylamine, triethylamine, etc.], picoline, 1, 5-diazabicyclo[4.3.0]-non-5-ene,, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo [5.4.0]undec-7-ene, or the like.

Suitable acid may include an organic acid [e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.], an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, hydrogen fluoride,, etc.] and an acid addition salt compound [e.g. pyridine hydrochloride, etc.].

The elimination using Lewis acid such as trihaloacetic acid [e.g. trichloroacetic acid, trifluoroacetic acid, etc.] or the like is preferablycarried out in the presence of cation trapping agents [e.g. anisole, phenol, etc.].

The reaction is usually carried out in a solvent such as water, an alcohol [e.g. methanol, ethanol, etc.], methylene chloride, diethtyl ether, dioxane, chloroform, tetrachloromethane, tetrahydrofuran, ethyl acetate, a mixture thereof or any other solvent which does not adversely, influence the reaction. A liquid base or acid can be also used as the solvent.

The reaction temperature is not critical and the reaction is usually carried out under cooling, at ambient temperature or under heating.

The reduction method applicable for the elimination reaction may include chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g. tin, zinc, iron, etc.] or metallic compound [e.g. chromium chloride, chromium acetate, etc.] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.].

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.]. palladium catalysts [e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.], nickel catalysts [e.g. reduced nickel, nickel oxide, Raney

nickel, etc.], cobalt catalysts [e.g. reduced cobalt, Raney cobalt, etc.], iron catalysts [e.g. reduced iron, Raney iron etc.], copper catalysts [e.g. reduced copper, Raney copper, Ullman copper, etc.] and the like.

The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, N,N-dimethylformamide, aceton, or a mixture thereof. Additionally, in case that the above-mentioned acid to be used in chemical reduction are in liquid, they can also be used as a solvent, Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, and other conventional solvent such as diethtyl ether, dioxane, tetrahydrofuran, etc., or a mixture thereof.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling , at ambient temperature or under heating.

Process 3

The compound (Id) or a salt thereof can be prepared by subjecting a compound (Ic) or a salt thereof to reduction reaction.

Suitable salts of the compounds (Ic) and (Id) can be referred to the ones as exemplified for the compound (I).

This reaction can be carried out in a similar manner to that of the aforementioned Process 2.

Process 4

The object compound (I) or a salt thereof can be prepared by reacting the compound (IV) or its reactive derivatives at the amino group or a salt thereof with the compound (V) or its reactive derivatives at the carboxy group or a salt thereof.

The starting compound (IV) or salts thereof are novel and can be prepared by the manners of Preparations mentioned below or a similar manner thereto.

Suitable salts of the compound (IV) and its reactive derivative can be referred to the ones as exemplified for the compound (I).

Suitable salts of the compound (V) and its reactive derivative may be a

base salt such as an alkali metal salt [e.g. sodium salt, pottassium salt, etc.], an alkaline earth metal salt [e.g. calcium salt, magnesium salt, etc.], an ammonium salt, an organic base salt [e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.], or the like, and an acid addition salt as exemplified for the compound (I).

This reaction can be carried out in a similar manner to that of the aforementioned Process 1.

The compounds obtained by the above processes can be isolated and purified by a conventional manner such as pulverization, recrystallization, column chromatography, reprecipitation, or the like.

The object compounds (I) thus obtained can be converted to its salt by a conventional manner.

The object compounds (I) and pharmaceutically acceptable salt thereof may include a solvate [e.g., enclosure compound (e.g., hydrate, etc.)].

The object compounds (I) and pharmaceutically acceptable salts thereof are expected to possess excellent pharmacological activities such as promotion activity of growth hormone release for animals and human bodies and they are useful for treatment of obesity in combination with an $\alpha 2$ or $\beta 3$ adrenergic agonist, osteoporosis in combination with parathyroid hormone, the catabolic effects of nitrogen wasting in combination with insulin-like growth factor 1, growth retardation, renal failure or insufficiency, schizophrenia, sleep disorder, skeletal dysplasia, depression, Alzheimer's disease, pulmonary dysfunction, hyperinsulinemia, ulcer, arthritis, cardiac dysfunction, replacement for elderly people, ALS, growth hormone deficient adults, physiological short stature including growth hormone deficient children , Turner's syndrome, intrauterine growth refardation, cachexia and protein loss due to cancer or AIDS and is also useful for stimulating the immune system, accelerating wound healing or bone fracture repair, improvement in muscle strength, and the like.

In order to illustrate the usefulness of the object compounds (I), the pharmacological test data of the representative compound of the compounds (I)

areshown in the following.

Test: Promotion activity of growth hormone release

(1)Test Method

Male wistar rats (6 week) were anaesthetized with ether. 0.6ml Blood samples were collected before and 5 min. after compounds injection. The secretagogues were given i.v. All compounds were dissolved in saline. Rat GH was measured by RIA (radioimmunoassay) in serum.

(2)Test compound

(a)2-amino-N-[1-[(1-Methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl) carbonyl]-2-(chroman-3-yl)ethyl]-2-methylpropanamide hydrochloride

(3)Test Result

Test Compound	Increasing ratio(%) of G.H. release
	1 mg/kg dosage
(a)	2932

G.H. = Growth Hormone

For therapeutic or preventive administration, the object compounds (I) of the present invention and pharmaceutically acceptable salts thereof are used in the form of the conventional pharmaceutical preparation which contains said compounds as an active ingredient, in admixture with a conventional pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral or external administration. If needed, there may be included in the above preparation auxiliary substance such as stabilizing agent, wetting or emulsifying agent, buffer or any other commonly used additives.

The effective ingredient may usually be administered with a unit dose of 0.001 mg/kg to 100 mg/kg/day, preferably 0.01 mg/kg to 50 mg/kg, 1 to 4 times a day. However, the above dosage may be increased or decreased according to age, weight and conditions of the patient or the administering method.

The following Preparations and Examples are given for the purpose of illustrating the present invention in more detail.

Preparation 1

A 0.98 M solution of diisobutylaluminum hydride in n-hexane (25.5 ml) was added dropwise to stirred solution of ethyl 2,3-tetrahydro-1-benzoxepin-4-carboxylate (2.18 g) in toluene (22 ml) at -70 - -50 ℃ in the presence of atmospheric N_2 gas over 30 minutes. The resulting mixture was stirred at the same temperature for 2 hours, allowed to stand at ambient temperature overnight, and added dropwise to stirred 1 N hydrochloric acid (100 ml) under ice cooling over 30 minutes. The organic layer was separated, washed with a 20 % aqueous solution of potassium sodium tartrate, aqueous sodium bicarbonate, and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was chromatographed (toluene - ethyl acetate) over silica gel to afford 2,3-tetrahydro-1-benzoxepinyl-4-methanol (942 mg) as a colorless oil.

IR(film): 3000 cm^{-1}.

^1H NMR($CDCl_3$) δ: 1.64(1H, s), 2.68(2H, t, J=4.7Hz), 4.21 - 4.30(4H, m), 6.38(1H, s), 6.92 - 7.19(4H, m).

(+)APCI MS m/z: 159(M^+ - OH).

Preparation 2

A solution of 2,3-dihydro-1-benzoxepinyl-4-methanol (0.90 g) and thionyl chloride (1.12 ml) in methylene chloride (18 ml) was stirred at ambient temperature overnight and evaporated in vacuo. The residue was extracted with ethyl acetate. The extract was washed with water (three times) and brine, dried over magnesium sulfate, and evaporated in vacuo to afford 4-chloromethyl-2,3-dihydro-1-benzoxepine (1.09 g) as a brown oil.

IR(film): 1600, 1565, 1260, 1235 cm^{-1}.

^{1}H NMR($CDCl_3$) δ: 2.79(2H, t, J=4.5Hz), 4.13 - 4.31(4H, m), 6.45(1H, s), 6.89 - 7.19 (4H, m).

(+)APCI MS m/z: 159(M^+ - Cl).

Preparation 3

A solution of N-benzalglycine methylester (1.18 g) in tetrahydrofuran (5 ml) was added dropwise to a stirred suspension of potassium tert-butoxide (0.75 g) in tetrahydrofuran (7 ml) at -70 ℃ and then a solution of 4-chloromethyl-2, 3-dihydro-1-benzoxepine (1.08 g) in tetrahydrofuran (5 ml) was added dropwise therein at the same temperature. The resulting mixture was stirred at same temperature for 2 hours. The additional N-benzalglycine methylester (1.18 g) and potassium tert-butoxide (0.75 g) were added to therein at the same temperature and the mixture was stirred at the same temperature for 1 hour. The reaction mixture was partitioned between diethyl ether and brine. The organic layer was separated, washed with water (three times) and brine, dried over magnesium sulfate, and evaporated in vacuo to afford methyl 2-(benzylideneamino)-3-(2, 3-dihydro-1-benzoxepin-4-yl)propionate (2.08 g) as a crude brown oil.

IR(film): 1725, 1635 cm^{-1}.

^{1}H NMR($CDCl_3$) δ: 2.65(2H, t, J=4.8Hz), 2.75(1H, dd, J=13.6, 8.4Hz), 2.93(1H, dd, J=13.6, 5.2Hz), 3.75(3H, s), 4.06 - 4.42(3H, m), 6.19(1H, s), 6.86 - 7.88(9H, m), 8.22(1H, s).

(+)APCI MS m/z: 336(M^+ + 1).

Preparation 4

A mixture of methyl 2-(benzylideneamino)-3-(2, 3-dihydro-1-benzoxepine-4-yl)propionate (2.08 g) and potassium bisulfate (2.53 g) in water (20 ml) was stirred at ambient temperature overnight, basified to pH 10 with 1 N NaOH, and extracted twice with ethyl acetate. The extracts were combined, dried over magnesium sulfate, and evaporated in vacuo. The residue was treated with 4 N HCl in ethyl acetate and the hydrochloride was washed with diethyl ether to methyl 2-amino-3-(2, 3-dihydro-1-benzoxepine-4-yl)propionate hydrochloride (0.68 g) as a pale yellow powder.

IR(film): 2550 - 2700, 1750, 1225 cm^{-1}.

^1H NMR($CDCl_3$) δ: 2.60(2H, m), 2.72(1H, d, J=7.8Hz), 3.72(3H, s), 4.17(2H, t, J=4.7Hz), 4.25(1H, m), 6.28(1H, s), 6.87 - 7.01(2H, m), 7.08 - 7.20(2H, m), 8.61(2H, m).

(+)APCI MS m/z: 248(M^+ + 1).

Preparation 5

1-Ethyl-3-(3'-dimethylaminopropyl)carbodiimide (410 mg) was added to a mixture of methyl 2-amino-3-(2, 3-dihydro-1-benzoxepine-4-yl)propionate hydrochloride (600 mg) , N-tert-butoxycarbonyl- α-methylalanine (494 mg), and 1-hydroxybenzotriazole (357 mg) in N, N-dimethylformamide (6 ml) at ambient temperature and the resulting mixture was stirred at the same temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with water (twice) and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was chromatographed (n-hexane - ethyl acetate) over silica gel to afford methyl 2-[[2-(tert-butoxycarbonylamino)-2, 2-dimethyl-1-oxoethyl]amino]-3-(2, 3-dihydro-1-benzoxepine-4-yl)propionate (763 mg) as a colorless amorphous powder.

IR(film): 3330, 1730, 1710, 1660 cm^{-1}.

^1H NMR($CDCl_3$) δ: 1.41(12H, s), 1.45(3H, s), 2.50 - 2.77(4H, m), 3.72(3H, s), 4.07 - 4.32(2H, m), 4.72 - 4.84(2H, m), 6.12(1H, s), 6.87 - 6.96(2H, m), 7.04 - 7.13(2H, m).

(+)APCI MS m/z: 433(M^+ + 1), 333.

Preparation 6

A solution of methyl 2-[[2-(tert-butoxycarbonylamino)-2, 2-dimethyl-1-oxoethyl]amino]-3-(2, 3-dihydro-1-benzoxepine-4-yl)propionate (750 mg) and lithium hydroxide (62 mg) in water (5 ml) and tetrahydrofuran (15 ml) was stirred overnight and evaporated in vacuo. The residue was partitioned between ethyl acetate and 0.1 N hydrochloric acid. The organic layer was washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was washed with n-hexane to afford 2-[[2-(tert-butoxycarbonylamino)-2, 2-dimethyl-1-

oxoethyl]amino]-3-(2,3-dihydro-1-benzoxepine-4-yl)propionic acid (764 mg) as a colorless powder.

IR(film): 3330, 1720, 1700, 1630 cm^{-1}.

^1H NMR($CDCl_3$) δ: 1.37(3H, s), 1.39(9H, s), 1.44(3H, s), 2.6 - 2.95(4H, m), 4.06 - 4.20(2H, m), 4.76(1H, m), 4.90(1H, br s), 6.17(1H, s), 6.89 - 6.97(2H, m), 7.06 - 7.15 (2H, m).

(+)APCI MS m/z: 419(M^+ + 1), 319.

Preparation 7

To a stirred solution of N-(diphenylmethylene)glycine methyl ester(66.4g) in teterahydrofuran(660ml) was added dropwise lithium bis(trimethylsilyl)amide (267.3ml, 1.0M solution in tetrahydrofuran) at -70℃ under nitrogen atmosphere, which was stirred for 1 hour at -70℃. The reatcion mixture was transferred via cannula to a stirred solution of 4-chloromethyl-2,3-dihydro-1-benzoxepine(51g) in tetrahydrofuran(510ml) at -70℃. After addition, the reaction mixture was allowed to warm to ambient temperature and stirred overnight. The reaction mixture was cooled to 5℃ and the reaction was quenched with 2N aqueous hydrochloric acid(700ml). The resulting mixture was stirred for 1.5 hours at ambient temperature. After the tetrahydrofuran was evaporated, the resulting aqueous solution was washed with ethyl acetate and the organic layer was reextracted with 2N aqueous hydrochloric acid. The aqueous layers were combined, washed with ethyl acetate and concentrated in vacuo. The residue was collected, washed with toluene and dried under reduced pressure to give methyl 2 -amino-3-(2,3-dihydro-1-benzoxepin-4-yl)propionate hydrochloride(69.0g) as a beige powder.

Preparation 8

1-Ethyl-3-(3'-dimethylaminopropyl)carbodimide(52.12ml) was added to a mixture of methyl 2-amino-3-(2,3-dihydro-1-benzoxepin-4-yl)propionate hydorchloride(67.5g), 1-hydroxybenzotriazole(38.6g) and acetic acid(15.0ml) at 5 ℃ with stirring. After addition, the reaction mixture was allowed to warm to ambient temperature and stirred for 3 hours. Insoluble material was filtered off and the filtrate was evaporated to give a residue, which was partitioned between

ethyl acetate and water. The organic layer was separated, washed in turn with water(twice), aqueous saturated sodium hydrogen carbonate (three times), and brine(twice), and dried over magnesium sulfate. Evaporation of the solvent gave methyl 2-acetylamino-3-(2,3-dihydro-1-benzoxepin-4-yl)propionate(64.65g) as a yellow powder.

m.p.; 82.0~83.0℃
FT IR(KBr);1749.1, 1641.1, 1535.1, 1490.7cm^{-1}
NMR($CDCl_3$) δ;1.99(3H, s), 2.54-2.77(4H, m), 3.73(3H, s), 4.10-4.30(2H, m), 4.74-4.85(1H, m), 6.03(1H, br-d, J=7.8Hz), 6.13(1H, s), 6.90-6.99(2H, m), 7.07-7.15 (2H, m).
(+)APCI MS m/z; 290(M^++1)

Preparation 9

To a stirred solution of methyl 2-acetylamino-3-(2,3-dihydro-1-benzoxepin-4-yl)propionate(64g) in 1,4-dioxane(650ml) was added a solution of lithium hydroxide(9.28g) in water (170ml) at 4℃, and then the reaction mixture was allowed to warm to 40℃ and stirred overnight. The dioxane was evaporated and remaining aqueous solution was washed with ethyl acetate. The organic layer was reextracted with 1N aqueous sodium hydroxide. The aqueous layers were combined, washed with ethyl acetate, and the pH was adjusted to 1.0 with conc-hydrochloric acid. The resulting solution was partitioned between ethyl acetate and water. The oraganic layer was collected, washed with water and dried over magnesium sulfate. Evaporation of the solvent gave 2-acethylamino-3-(2,3-dihydro-1-benzoxepin-4-yl)propionic acid(57.4g) as white powder.
m.p.; 165.0~166.0℃
FT IR(KBr);1727.9, 1608.3, 1565.9, 1540.8, 1490.7cm^{-1}
NMR(DMSO-d_6) δ;1.81(3H, s), 2.38-2.67(4H, m), 4.00-4.20(2H, m), 4.38-4.50(1H, m), 6.18(1H, s), 6.84-7.17(4H, m), 8.15(1H, d, J=8.1Hz), 12.6(1H, br-s)
(+)APCI MS m/z; 276(M^++1)

Preparation 10

2-Acetylamino-3-(2,3-dihydro-1-benzoxepin-4-yl)propionic acid(40g) was

dissolved in a mixture of 1N aqueous sodium hydroxide solution (160ml) and water (200ml), and which was adjusted to pH 8.0 with 1N aqueous hydrochloric acid. Then the resulting mixture was allowed to warm to 37℃, and to which was added cobalt (II) chloride hexahydrate (200mg) and Acylase(Acylase Amano, 2.0g). After being adjusted to pH 7.5, the reaction mixture was stirred for 24 hours while keeping the temperature at 37℃. To the resulting mixture was added water until insoluble material was disappeared, the pH was adjusted to 1.9 with conc-hydrochloric acid, which was partitioned between ethyl acetate and water. The organic layer was separated and the aqueous layer was reextracted with ethyl acetate. The organic layers and the aqueous layers were combined respectively.

The organic layer was washed with 1N aquous hydrochloric acid, water and brine, and dried over magnesium sulfate. Evaporation of the solvent gave crude (2R)-2-acetylamino-3-(2,3-dihydro-1-benzoxepin-4-yl)propionic acid as a foam (14.8g). The aqueous layer was washed with ethyl acetate, concentrated in vacuo, and azeotroped twice with toluene. The residue was collected, washed with toluene and dried under reduced pressure, which was dissolved in water. The resulting solution was adjusted to pH5.6 with pyridine. The precipitate was collected by filtration, washed with water, and dried under high vacuum to give (2S)-2-amino-3-(2,3-dihydro-1-benzoxepin-4-yl)propionic acid (9.5g). An analytical sample was obtained by recrystallization from water.

m.p.; 240℃(dec.)

FT IR(KBr);1600.6, 1517.7, 1492.6, 1442.5, 1409.7cm^{-1}

NMR(DMSO-d_6) δ;2.64-2.94(4H, m), 3.95(1H, dd, J=4.9Hz and 9.3Hz), 4.28-4.33(2H, m), 6.38(1H, s), 6.99-7.15(2H, m), 7.20-7.33(2H, m)

(+)APCI MS m/z; 234(M^++1)

$[\alpha]_D^{27.0}$-40.0° (C=0.5, 1N HClaq.).

Analysis: Calculated for $C_{13}H_{15}NO_3 \cdot 1/2H_2O$,

C, 64.45; H, 6.66;N, 5.78

Found C, 64.17; H, 6.63;N, 5.71

Preparation 11

Optically pure (2R)-2-acetylamino-3-(2,3-dihydro-1-benzoxepin-4-yl)-propionic acid was prepared from crude one according to substantially the same

procedure of enzymatic resolution as that of Preparation 10(17.5g) as a foam.
FT IR(KBr);1714.1, 1619.9, 1554.3, 1490.7, 1440.6, 1415.5cm^{-1}
NMR($CDCl_3$) δ;1.99(3H, s), 2.51-2.85(4H, m), 4.06-4.28(2H, m), 4.69-4.81(1H, m), 6.15(1H, s), 6.41(1H, d, J=7.7Hz), 6.80-6.97(2H, m), 7.05-7.13(2H, m).
(+)APCI MS m/z; 276(M$^+$+1)
$[\alpha]_D^{17.0}$-33.0° (C=1.0, CH_2Cl_2).

Preparation 12

A suspension of (2R)-2-acetylamino-3-(2,3-dihydro-1-benzoxepin-4-yl)-propionic acid (15.0g) in 2N aqueous hydrochloric acid (150ml) was heated at reflux for 4 hours. The reaction mixture was cooled to ambient temperature, washed twice with ethyl acetate, and concentrated in vacuo. The residue was azeotroped twice with toluene, collected by filtration, washed with toluene and ethyl ether, and dried under reduced pressure. The resulting material was dissolved in water (200ml), which was adjusted to pH 5.4 with pyridine. The precipitate was collected by filtration, washed with water and dried under high vacuum to give (2R)-2-amino-3-(2,3-dihydro-1-benzoxepin-4-yl)propionic acid (6.91g) as a white powder. An analytical sample was obtained by recrystallization from water.
m.p.; 236℃(dec.)
FT IR(KBr);1600.6, 1517.7, 1492.6, 1442.5cm^{-1}
NMR(DMSO-d_6) δ;2.64-2.94(4H, m), 3.95(1H, dd, J=4.9Hz and 9.3Hz), 4.28-4.33(2H, m), 6.38(1H, s), 6.99-7.15(2H, m), 7.20-7.33(2H, m)
(+)APCI/MS m/z; 234(M$^+$+1)
$[\alpha]_D^{17.0}$+38.6° (C=0.5, 1N HClaq.).
Analysis: Calculated for $C_{13}H_{15}NO_3 \cdot 1/2H_2O$,
C, 64.45; H, 6.66; N, 5.78
Found C, 64.58; H, 6.63; N, 5.73

Preparation 13

To a stirred mixture of (2R)-2-amino-3-(2,3-dihydro-1-benzoxepin-4-yl)-propionic acid(4.0g) and di-tert-butyl dicarbonate(3.6g) in water(40ml) and dioxane(40ml) was added triethylamine(2.63ml) at ambient temperature. After

stirring for 22 hours, the solvent was removed in vacuo. The residue was dissolved in water, to which was added ethyl acetate. The resulting mixture was adjusted to pH2.0 with 2N aqueous hydrochloric acid. The organic layer was separated, washed with 0.1N aqueous hydrochloric acid and brine, and dried over magnesium sulfate. Evaporation of the solvent gave (2R)-2-[(tert-butoxycarbonyl)-amino]-3-(2,3-dihydro-1-benzoxepin-4-yl)propionic acid(5.7g) as a foam.

FT IR(KBr):1716.3, 1606.4, 1567.8, 1513.8, 1492.6, 1442.5, 1402.0cm^{-1}

NMR($CDCl_3$) δ :1.38(9H, s), 2.40-2.90(4H, m), 4.15-4.30(2H, m), 4.40-4.60(1H, m), 5.00(1H, br-d, J=7.4Hz), 6.18(1H, s), 6.90-7.00(2H, m), 7.06-7.15(2H, m)

(+)APCI MS m/z; 234(M^+-CO_2Bu^t+1)

$[\alpha]_D^{20.0}$+12.4° (C=0.5, CH_2Cl_2)

Preparation 14

1-Ethyl-3-(3'-dimethylaminopropyl)carbodimide(1.1ml) was added to a stirred mixture of (2R)-2-[(tert-butoxycarbonyl)amino]-3-(2,3-dihydro-1-benzoxepin-4-yl)propionic acid(1.44g), 1-methanesulfonylspiro[indoline-3,4'-piperidine] hydrochloride(1.37g) and 1-hydroxybenzotriazole(700mg) in dichloromethane(50ml) at 5℃. The reaction mixture was allowed to warm to ambient temperature and stirred for 4 hours. Evaporation of the solvent gave a residue, which was partitioned between ethyl acetate and water. The organic layer was separated, washed in turn with 0.1N aqueous hydrochloric acid(twice), brine, saturated sodium hydrogen carbonate in water (twice) and brine (twice), and dried over magnesium sulfate. Evaporation of the solvent gave 1'-[(2R)-2-[(tert-butoxycarbonyl)amino]-3-(2,3-dihydro-1-benzoxepin-4-yl)propionyl]-1-methanesulfonylspiro[indoline-3,4'-piperidine](2.5g) as a foam.

FT IR(film):1706.1, 1641.1, 1602.6, 1490.7, 1450.2cm^{-1}

NMR($CDCl_3$)(mixture of rotamers) δ :1.36 and 1.40(9H(1:1), 2×s), 1.60-2.00(4H, m), 2.35-2.90(5H, m)2.88 and 2.91(3H(1:1), 2×s), 3.10-3.35(1H, m), 3.79 and 3.82(2H (1:1, 2×s), 3.90-4.40(3H, m), 4.60-4.75(1H, m), 4.80-5.00(1H, m), 5.30-5.50(1H, m), 6.18 and 6.25 (1H(1:1), 2×s), 6.39, 6.43 and 6.83-7.42(8H, m)

(+)APCI MS m/z; 482(M^+-CO_2Bu^t+1), 526(M^+-$C(CH_3)_3$+1), 582(M^++1)

Preparation 15

1'-[(2R)-2-[(tert-Butoxycarbonyl)amino]-3-(2,3-dihydro-1-benzoxepin-4-yl)-propionyl]-1-methanesulfonylspiro[indoline-3,4'-piperidine](1.9g) was dissolved in methanol, and 10% palladium on carbon (400mg, 50% wet) was added. The resulting mixture was stirred at ambient temperature under hydrogen atmosphere. After 4 hours, the catalyst was removed by filtration, and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel(230-400mesh) eluting with a mixture of toluene and ethyl acetate(6:1) to give two compounds; the less polar compound was 1'-[(2R)-2-[(tert butoxycarbonyl)amino]-3-[(4S)-2,3,4,5-tetrahydro-1-benzoxepin-4-yl]propionyl]-1-methanesulfonylspiro[indoline-3,4'-piperidine](550mg) as a foam, and the more polar compound was 1'-[(2R)-2-[(tert-butoxycarbonyl)amino]-3-[(4R)-2,3,4,5-tetrahydro-1-benzoxepin-4-yl]propionyl]-1-methanesulfonylspiro[indoline-3,4'-piperidine](670mg) as a foam.

1'-[(2R)-2-[(tert-Butoxycarbonyl)amino]-3-[(4S)-2,3,4,5-tetrahydro-1-benzoxepin-4-yl]propionyl]-1-methanesulfonylspiro[indoline-3,4'-piperidine]
FT IR(film);1702.8, 1639.2, 1484.9, 1450.2cm^{-1}
NMR($CDCl_3$)(mixture of rotamers) δ;1.41 and 1.42(9H(1:1), 2×s), 1.60-2.30(9H, m), 2.60-2.90(3H, m), 2.93(3H, s), 3.10-3.40(1H, m), 3.65-4.10(4H, m), 4.15-4.40(1H, m), 4.45-4.85(2H, m), 5.34(1H, d, J=9.6Hz), 6.90-7.50(8H, m)
(+)FAB MS m/z; 484(M^+-CO_2Bu^t+1), 584(M^++1)

1'-[(2R)-2-[(tert-butoxycarbonyl)amino]-3-[(4R)-2,3,4,5-tetrahydro-1-benzoxepin-4-yl]propionyl]-1-methanesulfonylspiro[indoline-3,4'-piperidine]
FT IR(film);1706.7, 1641.1, 1606.4, 1486.8, 1450.2cm^{-1}
NMR($CDCl_3$)(mixture of rotamers) δ;1.45(9H, s), 1.55-2.20(9H, m), 2.60-3.20(4H, m), 2.92(3H, s), 3.60-4.20(3H, m), 3.83(2H, s), 4.45-4.65(1H, m), 4.65-4.95(1H, m), 5.32(1H, d, J=8.8Hz), 6.90-7.50(8H, m)
(+)FAB MS m/z; 484(M^+-CO_2Bu^t+1), 584(M^++1)

Preparation 16

To a solution of 1'-[(2R)-2-[(tert-butoxycarbonyl)amino]-3-[(4S)-2,3,4,5-tetrahydro-1-benzoxepin-4-yl]propionyl]-1-methanesulfonylspiro[indoline-3,4'-piperidine](520mg) in dichloromethane(10ml) was added trifluoroacetic acid(690 μ

1), and stirred for 5 hours at ambient temperature. Evaporation of the solvent gave a residue, which was dissolved in ethyl acetate, washed with saturated sodium hydrogen carbonate in water and brine, and dried over magnesium sulfate. The solvent was evaporated to give 1'-[(2R)-2-amino-3-[(4S)-2,3,4,5-tetrahydro-1-benzoxepin-4-yl]propionyl]-1-methanesulfonylspiro[indoline-3,4'-piperidine] (330mg) as a foam.

FT IR(film);1639.2, 1602.6, 1483.0, 1454.1cm^{-1}

NMR($CDCl_3$)(mixture of rotamers) δ;1.40-2.20(9H, m), 2.60-2.90(3H, m)2.93(3H, s), 3.05-3.35(1H, m), 3.70-4.00(5H, m), 4.10-4.35(1H, m), 4.50-4.80(1H, m), 6.85-7.45 (8H, m)

(+)FAB MS m/z; 484(M^++1)

Preparation 17

1'-[(2R)-2-Amino-3-[(4R)-2,3,4,5-tetrahydro-1-benzoxepin-4-yl]propionyl] -1-methanesulfonylspiro[indoline-3,4'-piperidine] was prepared according to a similar manner to that of Preparation 16 as a foam.

FT IR(film);1633.4, 1481.1, 1454.1, 1346.1cm^{-1}

NMR($CDCl_3$)(mixture of rotamers) δ;1.40-2.35(9H, m), 2.55-3.10(4H, m), 2,92(3H, s), 3.40-3.60(1H, m), 3.70-4.20(5H, m), 4.50-4.75(1H, m), 6.85-7.45(8H, m).

(+)FAB MS m/z; 484(M^++1)

Preparation 18

(2S)-2-[(tert-Butoxycarbonyl)amino]-3-(2,3-dihydro-1-benzoxepin-4-yl)-propionic acid was prepared according to a similar manner to that of Preparation 13 as a foam.

FT IR(KBr);1718.6, 1608.3, 1567.8, 1494.6cm^{-1}

NMR($CDCl_3$) δ;1.38(9H, s), 2.40-2.90(4H, m), 4.15-4.30(2H, m), 4.40-4.60(1H, m), 5.00(1H, br-d, J=7.4Hz), 6.18(1H, s), 6.90-7.00(2H, m), 7.06-7.15(2H, m).

(+)APCI MS m/z;234(M^+-CO_2Bu^t+1),

$[\alpha]_D^{20.0}$-12.2° (C=0.5, CH_2Cl_2)

Preparation 19

1'-[(2S)-2-[(tert-Butoxycarbonyl)amino]-3-(2,3-dihydro-1-benzoxepin-4-yl)

propionyl]-1-methanesulfonylspiro[indoline-3,4'-piperidine] was prepared according to a similar manner to that of Preparation 14 as a foam.
FT IR(film)1706.7, 1641.1, 1602.6, 1569.8, 1488.8, 1452.1cm^{-1}
NMR($CDCl_3$)(mixture of rotamers) δ;1.36 and 1.40(9H(1:1), 2×s), 1.60-2.00(4H, m), .2.35-2.90(5H, m), 2.88 and 2.91(3H(1:1), 2×s), 3.10-3.35(1H, m), 3.79 and 3.82 (2H(1:1), 2×s), 3.90-4.00(3H, m), 4.60-4.75(1H, m), 4.80-5.00(1H, m), 5.30-5.50 (1H, m), 6.18 and 6.25(1H(1:1), 2×s), 6.39, 6.43 and 6.83-7.42(8H, m).
(+)APCI MS m/z;482(M$^+$-CO_2Bu^t+1), 526(M$^+$-$C(CH_3)_3$+1), 582(M$^+$+1).

Preparation 20

1'-[(2S)-2-[(tert-Butoxycarbonyl)amino]-3-[(4R)-2,3,4,5-tetrahydro-1-benzoxepin-4-yl]propionyl]-1-methanesulfonylspiro[indoline-3,4'-piperidine] as the less polar compound and 1'-[(2S)-2-[(tert-butoxycarbonyl)amino]-3-[(4S)-2,3,4,5-tetrahydro-1-benzoxepin-4-yl]propionyl]-1-methanesulfonylspiro-[indoline-3,4'-piperidine] as the more polar compound were prepared according a similar manner to that of Preparation 15.

1'-[(2S)-2-tert-Butoxycarbonylamino-3-[(4R)-2,3,4,5-tetrahydro-1-benzoxepin-4-yl]propionyl]-1-methanesulfonylspiro[indoline-3,4'-piperidine].
FT IR(film);1706.7, 1641.1, 1602.6, 1488.8, 1450.2cm^{-1}
NMR($CDCl_3$)(mixture of rotamers) δ; 1.41 and 1.42(9H(1:1), 2×s), 1.60-2.30(9H, m), 2.60-2.90(3H, m), 2.93(3H, s), 3.10-3.40(1H, m), 3.65-4.10(4H, m), 4.15-4.40 (1H, m), 4.45-4.85(2H, m), 5.34(1H, d, J=9.0Hz), 6.90-7.50(8H, m),
(+)FAB MS m/z;484(M$^+$-CO_2Bu^t+1), 584(M$^+$+1)

1'-[(2S)-2-tert-Butoxycarbonylamino-3-[(4S)-2,3,4,5-tetrahydro-1-benzoxepin-4-yl]propionyl]1-methanesulfonylspiro[indoline-3,4'-piperidine].
FT IR(film);1704.8, 1641.1, 1486.8, 1452.1cm^{-1}
NMR($CDCl_3$)(mixture of rotamers) δ;1.45(9H, s), 1.55-2.20(9H, m), 2.60-3.20(4H, s), 2.92(3H, s), 3.60-4.20(3H, m), 3.83(2H, s), 4.45-4.65(1H, m), 4.65-4.95(1H, m), 5.32(1H, br-d, J=5.3Hz), 6.90-7.50(8H, m).
(+)FAB MS m/z;484(M$^+$-CO_2Bu^t+1), 584(M$^+$+1)

Preparation 21

1'-[(2S)-2-Amino-3-[(4R)-2,3,4,5-tetrahydro-1-benzoxepin-4-yl]-propionyl]

-1-methanesulfonylspiro[indoline-3,4'-piperidine] was prepared according to a similar manner to that of Preparation 16 as a foam.
FT IR(film);1704.8, 1639.2, 1483.0, 1452.1cm^{-1}
NMR($CDCl_3$)(mixture of rotamers) δ; 1.40-2.20(9H, m), 2.60-2.90(3H, m), 2.93(3H, s), 3.05-3.35(1H, m), 3.70-4.00(5H, m), 4.10-4.35(1H, m), 4.50-4.80(1H, m), 6.85-7.45(8H, m).
(+)FAB MS m/z;484(M^++1)

Preparation 22

1'-[(2S)-2-Amino-3-[(4S)-2,3,4,5-tetrahydro-1-benzoxepin-4-yl]-propionyl]-1-methansulfonylspiro[indoline-3,4'-piperidine] was prepared according to a similar manner to that of Preparation 16 as a foam.
FT IR(film);1637.3, 1483.0, 1454.1cm^{-1}
NMR($CDCl_3$)(mixture of rotameres) δ; 1.40-2.35(9H, m), 2.55-3.10(4H, m), 2.92(3H, s), 3.40-3.60(1H, m), 3.70-4.20(5H, m), 4.50-4.75(1H, m), 6.85-7.45(8H, m).
(+)FAB MS m/z;484(M^++1)

Preparation 23

1'-[(2R)-2-Amino-3-(2,3-dihydro-1-benzoxepin-4-yl)propionyl]-1-methanesulfonylspiro[indoline-3,4'-piperidine] was prepared according to the similar manner as that of Preparation 16 as a foam.
FT IR(film); 1637.3, 1569.8, 1481.1, 1456.0cm^{-1}.
NMR($CDCl_3$)(mixture of rotamers) δ; 1.50-3.00(9H, m), 2.88 and 2.91(3H(1:1), 2×S), 3.10-3.30(1H, m), 3.65-4.40(6H, m), 4.45-4.75(1H, m), 6.27(1H, s), 6.38-6.43 and 6.80-7.40(8H, m).
(+)FAB MS m/z; 482(M^++1).

Preparation 24

1'-[(2s)-2-Amino-3-(2,3-dihydro-1-benzoxepin-4-yl)propionyl]-1-methanesulfonylspiro[indoline-3,4'-piperidine] was prepared according to the similar manner as that of Preparation 16 as a foam.
FT IR(film); 1635.3, 1569.8, 1481.1, 1456.0cm^{-1}.
NMR($CDCl_3$)(mixture of rotamers) δ; 1.50-3.00(9H, m), 2.88 and 2.91(3H(1:1), 2×

s), 3.10-3.30(1H, m), 3.65-4.40(6H, m), 4.45-4.75(1H, m), 6.27(1H, s), 6.38-6.43 and 6.80-7.40(8H, m).
(+)FAB MS m/z; 482(M^++1).

Preparation 25

Ethyl 3-benzyl-1-[(2R)-2-tert-butoxycarbonylamino-3-(2,3-dihydro-1-benzoxepin-4-yl)propionyl]piperidine-3-carboxylate was prepared according to the similar manner as that of Preparation 14, except substituting ethyl 3-benzylpiperidine-3-carboxylate hydrochloride for 1-methanesulfonylspiro[indoline-3,4'-piperidine]hydrochloride, as a foam.
FT IR(KBr); 1714.4, 1645.0, 1490.7, 1454.1, 1442.5cm^{-1}.
NMR($CDCl_3$)(mixture of rotamers) δ; 1.05-1.80(16H, m), 2.00-3.70(8H, m), 4.00-5.60(8H, m), 6.05-6.25(1H, m), 6.80-7.30(9H, m).
(+)APCI MS m/z; 463($M^+-CO_2Bu^t$+2, 507($M^+-C(CH_3)_3$+2), 563(M^++1).

Preparation 26

Ethyl 1-[(2R)-2-amino-3-(2,3-dihydro-1-benzoxepin-4-yl)propionyl]-3-benzylpiperidine-3-carboxylate was prepared according to a similar manner to that of Preparation 16 as an oil.
FT IR(neat); 1724.1, 1643.1, 1490.7, 1454.1, 1442.5cm^{-1}.
NMR($CDCl_3$)(mixture of rotamers) δ; 1.12-1.21(3H, m), 1.35-3.70(12H, m), 3.80-4.70(7H, m), 6.10-6.25(1H, m), 6.10-6.25(9H, m).
(+)APCI MS m/z; 463(M^++1).

Preparation 27

2-Amino-3-(benzofuran-2-yl)propionic acid hydrochloride was prepared according to a similar manner to that of Preparation 7 as a white powder.
FT IR(KBr); 1736, 1643, 1489, 1452, 1408, 1223, 1197, 1169cm^{-1}.
^{1}HNMR(D_2O) δ; 3.47-3.56(2H, m), 4.34(1H, t, J=5, 5Hz), 6.79(1H, s), 7.26-7.66(4H, m)
(+)APCI MS m/z; 206(M^++1).

Preparation 28

3-(Benzofuran-2-yl)-2-tert-butoxycarbonylaminopropionic acid was prepared according to a similar manner to that of Preparation 13 as a white powder.

FT IR(KBr): 1736, 1686, 1537, 1250, 1169cm^{-1}.

^{1}HNMR(DMSO-d_6) δ ; 1.46(9H, s), 3.00-3.30(2H, m), 4.20-4.40(1H, m), 6.13(1H, br-s), 6.63(1H, s), 7.15-7.27(2H, m), 7.47-7.60(2H, m), 12.77(1H, br-s).

Preparation 29

1'-[2-tert-Butoxycarbonylamino-3-(benzofuran-2-yl)propionyl]-1-methanesulfonylspiro[indoline-3,4'-piperidine] was prepared according to a similar manner to that of Preparation 14 as a foam.

FT IR(KBr): 1708, 1639, 1512, 1456, 1350, 1252, 1161cm^{-1}.

^{1}HNMR($CDCl_3$) δ ; 1.40-2.00(13H, m), 2.60-3.30(6H, m), 3.60-3.85(2H, m), 4.00-4.15(1H, m), 4.20-4.70(2H, m), 5.00-5.60(2H, m), 6.00-7.60(9H, m).

Preparation 30

1'-[2-Amino-3-(benzofuran-2-yl)propionyl]-1-methanesulfonylspiro-[indoline-3,4'-piperidine]was prepared according to a similar manner to that of Preparation 16 as a foam.

FT IR(film): 1732, 1637, 1477, 1456, 1346, 1252, 1159cm^{-1}.

^{1}HNMR($CDCl_3$) δ ; 1.40-2.20(4H, m), 2.60-3.30(7H, m), 3.70-4.10(3H, m), 4.20-4.45(1H, m), 4.55-4.75(1H, m), 6.25-7.60(9H, m).

(+)APCI MS m/z; 454(M^++1).

Preparation 31

2-(2,3,4,5-Tetrahydro-1-benzoxepin-5-yl)ethanol was prepared according to a similar manner to that of Preparation 47 as an oil.

FT IR(neat): 2935, 2871, 1736, 1485, 1446, 1236, 1051cm^{-1}.

^{1}HNMR($CDCl_3$) δ ; 1.60-1.95(4H, m), 2.09-2.35(2H, m), 3.00-3.10(1H, m), 3.40-3.70(3H, m), 4.25-4.36(1H, m), 6.90-7.20(4H, m).

(+)APCI MS m/z; 193(M^++1).

Preparation 32

2-(2, 3, 4, 5-tetrahydro-1-benzoxepin-5-yl) methanesulfonate was prepared from 2-(2, 3, 4, 5-tetrahydro-1-benzoxepin-5-yl) ethanol by a conventional method as a foam.

FT IR(film); 2952, 1490, 1450, 1346, 1334, 1236, 1166cm^{-1}.

^{1}HNMR($CDCl_3$) δ ; 1.70-2.44(6H, m), 2.94(3H, s), 3.00-3.15(1H, m), 3.55-3.68(1H, m), 3.90-4.05(1H, m), 4.10-4.20(1H, m), 4.30-4.45(1H, m), 6.96-7.21(4H, m).

(+)APCI MS m/z; 271(M^++1).

Preparation 33

5-(2-Iodoethyl)-2, 3, 4, 5-tetrahydro-1-benzoxepine was prepared from 2-(2, 3, 4, 5-tetrahydro-1-benzoxepin-5-yl) methanesulfonate by a conventional method as an oil.

FT IR(neat); 1716, 1698, 1683, 1653, 1559, 1540, 1508, 1456cm^{-1}.

^{1}HNMR($CDCl_3$) δ ; 1.70-2.55(6H, m), 2.84-3.17(3H, m), 3.60(1H, dt, J=1.8, 11.6Hz), 4.30-4.39(1H, m), 6.95-7.22(4H, m).

(+)APCI MS m/z; 303(M^++1).

Preparation 34

2-Acetylamino-2-[2-(2, 3, 4, 5-tetrahydro-1-benzoxepin-5-yl)ethyl]malonic acid diethyl ester was prepared from 5-(2-iodoethyl)-2, 3, 4, 5-tetrahydro-1-benzoxepine by a conventional method as a white solid.

FT IR(KBr); 3257, 1753, 1741, 1643, 1547, 1487, 1373, 1234, 1207cm^{-1}.

^{1}HNMR($CDCl_3$) δ ; 1.11-1.34(6H, m), 1.40-2.30(11H, m), 2.70-2.90(1H, m), 3.50-3.70 (1H, m), 4.08-4.40(4H, m), 4.50-4.70(1H, m), 5.90-6.05(1H, m), 6.77-7.20(4H, m).

(+)APCI MS m/z; 392(M^++1).

Preparation 35

2-Acetylamino-4-(2, 3, 4, 5-tetrahydro-1-benzoxepin-5-yl)butyric acid was prepared from 2-acetylamino-2-[2-(2, 3, 4, 5-tetrahydro -1-benzoxepin-5-yl) ethyl] malonic acid diethyl ester by a conventional method as a white solid.

FT IR(KBr); 3020, 1732, 1718, 1670, 1541, 1522, 1489, 1215cm^{-1}.

^{1}HNMR($CDCl_3$) δ ; 1.30-2.30(11H, m), 2.79(1H, br-s), 3.62(1H, t, J=11.5Hz), 4.25-4.

40(1H, m), 4.45-4.65(1H, m), 6.10(1H, dd, J=7.7, 13.1Hz), 6.94-7.17(4H, m).
(+)APCI MS m/z; 292(M'+1).

Preparation 36

2-Amino-4-(2,3,4,5-tetrahydro-1-benzoxepin-5-yl)butyric acid hydrochloride was prepared from 2-acetylamino-4-(2,3,4,5-tetrahydro-1-benzoxepin-5-yl)butyric acid by a conventional method as a white solid.
FT IR(KBr); 3415, 2933, 1751, 1531, 1487, 1448, 1236, 1217cm^{-1}.
^{1}HNMR(CD_3OD) δ; 1.50-2.40(8H, m), 2.75-2.90(1H, m), 3.60(1H, t, J=11.8Hz), 3.85-4.00(1H, m), 4.25-4.40(1H, m), 6.90-7.02(2H, m), 7.09-7.17(2H, m).
(+)APCI MS m/z; 250(M'+1).

Preparation 37

2-tert-Butoxycarbonylamino-4-(2,3,4,5-tetrahydro-1-benzoxepin-5-yl)-butyric acid was prepared from 2-amino-4-(2,3,4,5-tetrahydro-1-beneoxepin-5-yl) butyric acid hydrochloride by a conuentional method as a foam.
FT IR(film); 3566, 1716, 1698, 1558, 1540, 1456, 1165, 1055cm^{-1}.
^{1}HNMR($CDCl_3$) δ; 1.44(9H, s), 1.60-2.30(8H, m), 2.70-2.90(1H, m), 3.55-3.70(1H, m), 4.20-4.40(2H, m), 4.90-5.05(1H, m), 6.94-7.20(4H, m).
(+)APCI MS m/z; 250(M'-CO_2 ^{t}Bu+2).

Preparation 38

1-Ethyl-3-(3'-dimethylaminopropyl)carbodiimide(0.34ml) was added to a mixture of 2-tert-butoxycarbonylamino-4-(2,3,4,5-tetrahydro-1-benzoxepin-5-yl)-butyric acid(470mg), 1-methanesulfonylspiro[indoline-3,4'-piperidine] hydrochloride(436mg) and 1-hydroxybenzotriazole(162mg) in dichloromethane(20ml) at ambient temperature, and the resulting mixture was stirred at the same temperature overnight.
The reaction mixture was partitioned between ethyl acetate and water.
The organic layer was separated, washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo to give residue.
Trifluoroacetic acid(2mg) was added to a solution of the residue
in dichloromethane(20mg) at ambient temperature, and the resulting mixture was

stirred at the same temperature overnight.
The reaction mixture was evaporated in vacuo and partitioned between ethyl acetate and saturated sodium hydrogen carbonate in water. The organic layer was separated, washed with water and brine, dried over magunesium sulfate, and evaporated in vacuo to give 1'-[2-amino-4-(2,3,4,5-tetrahydro-1-benzoxepin-5-yl)-butyryl]-1-methanesulfonylspiro[indoline-3,4'-piperidine](530mg) as a foam.
IR(film); 2931, 1641, 1487, 1460, 1348, 1236, 1161, 1047cm^{-1}.
^{1}HNMR($CDCl_3$) δ ; 1.30-3.20(18H, m), 3.40-4.10(5H, m), 4.20-4.70(2H, m), 6.85-7.45 (8H, m).
(+)APCI MS m/z ; 498(M^++1).

Preparation 39

3-(Methanesulfonyloxymethyl) chroman was prepared from (chroman-3-yl) methanol by a conventional method method as a white powder.
FT IR(KBr); 2939, 1493, 1458, 1348, 1227, 1173, 1124cm^{-1}.
^{1}HNMR($CDCl_3$) δ ; 2.49-2.71(2H, m), 2.94-3.02(4H, m), 4.03-4.27(4H, m), 6.80-6.91 (2H, m), 7.04-7.15(2H, m).
(+)APCI MS m/z; 243(M^++1).

Preparation 40

3-(Iodomethyl)chroman(4.3g) was prepared from 3-(methanesulfonyloxy methyl) choroman by a conventional as an oil.
FT IR(neat); 2322, 1508, 1489, 1456, 1246, 1225, 1184cm^{-1}.
^{1}HNMR($CDCl_3$) δ ; 2.26-2.34(1H, m), 2.64(1H, dd, J=16.4, 7.9Hz), 3.00(1H, dd, J=16.4, 5.5Hz), 3.15-3.30(2H, m), 4.25-4.33(1H, m), 6.80-6.90(2H, m), 7.04-7.14(2H, m).
(+)APCI MS m/z; 274(M^++1).

Preparation 41

2-Acetylamino-2-[(chroman-3-yl)methyl]malonic acid diethyl ester was prepared from 3-(iodomethyl) chroman by a conventional method as a white solid.
FT IR(KBr); 1756, 1741, 1682, 1668, 1654, 1508, 1490, 1371, 1226cm^{-1}.
^{1}HNMR($CDCl_3$) δ; 1.22-1.34(6H, m), 1.95-2.08(5H, m), 2.36-2.55(3H, m), 2.70-2.74 (1H, m), 3.72(1H, dd, J=10.6, 9.3Hz), 4.06-4.14(1H, m), 4.20-4.33(4H, m), 6.47 (1H, br-s), 6.75-7.11(4H, m).
(+)APCI MS m/z; 364(M^++1).

Preparetion 42

2-Acetylamino-3-(chroman-3-yl)propionic acid was prepared from 2-acetylamino-2-[(chroman-3-yl)methyl] malonic acid diethyl ester by a conventional method as an oil.
FT IR(neat); 3332, 1707, 1619, 1562, 1489, 1454, 1226cm^{-1}.
^{1}HNMR($CDCl_3$) δ; 1.75-1.77(1H, m), 2.05(3H, s), 2.90-3.96(1H, m), 3.78-3.88(1H, m), 4.07-4.18(1H, m), 4.55-4.58(2H, m), 6.37-6.41(1H, m), 6.77-7.04(4H, m).
(+)APCI MS m/z; 264(M^++1).

Preparation 43

2-Amino-3-(chroman-3-yl)propionic acid hydrochloride was prepared from 2 -acetylamino-3-(chroman-3-yl) propionic acid by a conventional method as a white solid.
^{1}HNMR(D_2O) δ; 1.84-2.06(2H, m), 2.26-2.28(1H, m), 2.59(1H, dd, J=16.4, 7.7Hz), 3.02(1H, d, J=16.4Hz), 3.89-4.11(2H, m), 4.25(1H, d, J=10.9Hz), 6.82-7.17(4H, m).
(+)APCI MS m/z; 222(M^++1).

Preparation 44

2-tert-Butoxycarbonylamino-3-(chroman-3-yl)propionic acid was prepared from 2-amino-3-(chroman-3-yl) propionic acid hydrochloride by a conventional method as an oil.
FT IR(neat); 2978, 1749, 1666, 1660, 1535, 1369, 1296, 1228, 1165cm^{-1}.
^{1}HNMR($CDCl_3$) δ; 1.44(9H, s), 1.66-1.93(2H, m), 1.99-2.05(1H, m), 2.45-2.60(1H, m), 2.93-3.01(1H, m), 3.71-3.87(1H, m), 4.11-4.26(2H, m), 5.00-5.03(1H, m), 6.77

-7.12(4H, m).
(+)APCI MS m/z; 222(M^+-CO_2^tBu+2).

Preparation 45

1'-[2-tert-Butoxycarbonylamino-3-(chroman-3-yl)propionyl]-1-methanesulfonylspiro[indoline-3,4'-piperidine] was prepared according to a similar manner to that of Preparation 14 as a foam.
FT IR(film); 2931, 1711, 1641, 1491, 1456, 1350, 1228, 1161cm^{-1}.
^{1}HNMR($CDCl_3$) δ; 1.45(9H, d, J=2.3Hz), 1.52-1.95(6H, m), 2.24-2.26(1H, m), 2.42-2.80(2H, m), 2.91(3H, d, J=1.1Hz), 3.04-3.27(2H, m), 3.61-4.35(5H, m), 4.55-4.81(2H, m), 5.42-5.51(1H, m), 6.78-7.42(8H, m).

Preparation 46

1'-[2-Amino-3-(chroman-3-yl)propinyl]-1-methanesulfonylspiro-[indoline-3,4'-piperidine] was prepared according to a similar manner to that of Preparation 16 as a foam.
FT IR(film); 2925, 1641, 1490, 1479, 1444, 1346, 1226, 1159, 1117cm^{-1}.
^{1}HNMR($CDCl_3$) δ; 1.45-2.04(6H, m), 2.49-2.90(5H, m), 2.91(3H, s), 3.00-3.06(2H, m), 3.80-4.29(5H, m), 4.57-4.59(1H, m), 6.67-7.41(8H, m).

Preparation 47

To a suspension of lithium aluminum hydride(1.36g) in tetrahydrofuran (100ml) was added carefully ethyl 2,3-dihydro-1-benzoxepin-4-carboxylate(4g) at 0℃ under nitrogen atomosphere. After stirring for 2 hours at ambient temperature, the reaction mixture was added in turn with water(1.36ml), 4N-aqueous sodium hydride solution(1.36ml) water(2.7ml) and magnesium sulfate. Insoluble material was removed by filtration and the filtrate was concentrated in vacuo to give (2,3,4,5-tetrahydro-1-benzoxepin-4-yl)methanol(2.57g).
^{1}HNMR($CDCl_3$) δ; 1.47(1H, t, J=5.2Hz), 1.70-2.04(3H, m), 2.68-2.84(2H, m), 3.58(2H, t, J=5.5Hz), 3.73-3.80(1H, m), 4.31-4.41(1H, m), 6.94-7.01(2H, m), 7.09-7.18(2H, m).
(+)APCI MS m/z; 179(M^++1).

Preparation 48

To a solution of oxalyl chloride(1.5ml) in dichloromethane(50ml)was added dropwise in turn with dimethylsulfoxide(2.35ml), (2,3,4,5-tetrahydro-1-benzoxepin-4-yl)methanol(2.57ml) and triethylamine(10ml) at -70℃ under nitrogen atmosphere. The reaction mixture was allowed to warm to ambient temperature and precipitate was removed by filtration. The filtrate was concentrated to give residue, which was dissolved in ethyl acetate, washed in turn with water, 1N-aqueous hydrochloric acid, brine, saturated sodium hydrogencarbonate in water and brine, and dried over magnesium sulfate. Evaporation of the solvent gave a residue, which was chromatographed on silica gel eluting with 10% ethyl acetate in n-hexane to give 2,3,4,5-tetrahydro-1-benzoxepine-4-carbaldehyde(1.97g).
^{1}HNMR($CDCl_3$) δ ; 2.06-2.22(2H, m), 2.48-2.61(1H, m), 2.92-3.15(2H, m), 3.76-3.88 (1H, m), 4.30-4.40(1H, m), 6.98-7.26(4H, m), 9.76(1H, s).

Preparation 49

A stirred suspension of 2,3,4,5-tetrahydro-1-benzoxepine-4-carbaldehyde (1.9g), sodium cyanide(1.58g), and ammonium carbonate(10.1g) in a mixture of methanol(40ml) and water(40ml) was refluxed for 18 hours. Methanol was evaporated in vacuo, and the remaining was allowed to stand at 0℃ and stirred for 3 hours. The insoluble material was collected by filteration, washed with water and dried to give 5-(2,3,4,5-tetrahydro-1-benzoxepin-4-yl)imidazolidine-2,4-dione(1.2g) as a solid.
FT IR(KBr); 1753, 1726, 1714, 1452, 1415, 1321, 1194cm^{-1}.
^{1}HNMR(DMSO-d_6) δ ; 1.90-1.93(3H, m), 2.36-2.43(1H, m), 2.69-2.82(1H, m), 3.60(1H, m), 4.11(1H, m), 4.33-4.40(1H, m), 6.90-7.13(4H, m), 8.09(1H, s), 10.73(1H, s).

Preparation 50

5-(2,3,4,5-Tetrahydro-1-benzoxepin-4-yl)imidazolidine-2,4-dione(1.2g) was hydrolyzed with a suspension of calcium hydroxide(1g) in water(20ml) at 130℃ in a sealed tube for 6 hours. Insoluble material was removed by filtration. To the filtrate was added di-tert-butyldicarbonate(1.3g), triethylamine(2ml) and 1.4-dioxane(30ml), and the mixture was stirred for 18 hours at ambient temperature. Evaporation of the solvent gave a residue, which was acidified to pH2 with 1N-

hydrochloric acid and extracted twice with ethyl acetate. The extracts were combined, dried over magnesium sulfate, and evaporated in vacuo to give tert-butoxycarbonylamino-(2,3,4,5-tetrahydro-1-benzoxepin-4-yl)acetic acid (1.78g) as an oil.

^{1}HNMR($CDCl_3$) δ ; 1.46(9H, s), 1.77-2.21(2H, m), 2.44-2.83(2H, m), 3.37-3.70(1H, m), 4.11-4.30(2H, m), 4.38-4.79(1H, m), 5.15-5.23(1H, m), 6.95-7.18(4H, m).

Preparation 51

1'-[2-tert-Butoxycarbonylamino -3-(2,3,4,5-tetrahydro-1-benzoxepin-4-yl) acetyl]-1-methanesulfonylspiro[indoline-3,4'-piperidine] was prepared according to a similar manner to that of Preparation 14 as a foam.

FT IR(film); 2933, 1710, 1639, 1631, 1479, 1459, 1226, 1047cm^{-1}.

^{1}HNMR($CDCl_3$) δ ; 1.45(9H, s), 1.49-1.94(6H, m), 2.75-3.26(8H, m), 3.74-4.68(7H, m), 5.42-5.52(1H, m), 6.94-7.41(8H, m).

Preparation 52

1'-[2-Amino-3-(2,3,4,5-tetrahydro-1-benzoxepin-4-yl)acetyl]-1-methanesulfonylspiro[indoline-3,4'-piperidine] was prepared according to a similar manner to that of Preparation 16 as a foam.

FT IR(film); 2923, 1730, 1641, 1631, 1479, 1462, 1346, 1226, 1159cm^{-1}.

^{1}HNMR($CDCl_3$) δ ; 1.45-2.05(6H, m), 2.57-2.85(5H, m), 2.91(3H, s), 2.92-3.10(2H, m), 3.84-4.07(5H, m), 4.38(1H, m), 4.69(1H, m), 6.93-7.41(8H, m).

Preparation 53

An emulsion of 2,3-dihydro-1-benzoxepine-4-carboxylic acid ethyl ester(2.20g) in 1N sodium hydroxide aqueous solution(12.1ml) and methanol(33ml) was stirred at room temperature for 19 hours and mixed with 1N hydrochloric acid(13.1ml). The resulting mixture was evaporated in vacuo. The residue was partitioned between ethyl acetate and brine. The organic layer was separated, washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residual solid was washed with n-hexane to afford 2,3-dihydro-1-benzoxepine-4-carboxylic acid(1.78g) as a colorless powder; mp168-169℃.

IR(Nujol); 1655, 1265cm^{-1}.

^{1}HNMR($CDCl_3$) δ ;2.99(2H, m), 4.30(2H, m), 6.97-7.08(2H, m), 7.23-7.38(2H, m), 7.72 (1H, s).
(+)APCI MS m/z; 173(M'-OH).

Preparation 54

A mixture of 2,3-dihydro-1-benzoxepine-4-carboxylic acid(2.71g), [(S)-2, 2'-bis(diphenylphosphino)-1,1'-binaphthyl]ruthenium(Ⅱ)acetate(78mg), and methanol(71ml) was heated in the presence of hydrogen at a pressure of 50atm at 50℃ for 16 hours. The reaction mixture was worked up in a usual manner to afford (S)-2,3,4,5-tetrahydro-1-benzoxepine-4-carboxylic acid(2.74g) as a crude powder, which was recrystallized from n-hexane-ethyl acetate. The precipitate(0.94g) was filtered off and the filtrate was evaporated in vacuo. The residue was chromatographed(chloroform-methanol) over silica gel to afford a solid(1.54g), which was dissolved in a solution of (R)-1-phenylethylamine(825mg) in chloroform. The resulting solution was evaporated in vacuo and the residue was recrystallized from ethanol to afford(R)-1-phenylethylamine/(S)-2,3,4,5-tetrahydro-1-benzoxepine-4-carboxylate(1.58g) as a colorless crystals, which was partitioned between ethyl acetate and 1N hydrochloric acid. The organic layer was washed with brine, dried over sodium sulfate, and evaporated in vacuo to afford (S)-2,3,4,5-tetrahydro-1-benzoxepine-4-carboxylic acid(0.92g) as a colorless powder.
IR(Nujol); 1725, 1685, 1245, 1220cm^{-1}.
^{1}HNMR($CDCl_3$) δ ; 2.02-2.30(2H, m), 2.64-2.78(1H, m), 2.99-3.22(2H, m), 3.75-3.88 (1H, m), 4.26-4.37(1H, m), 6.96-7.05(2H, m), 7.12-7.21(2H, m).

Preparation 55

1.0M solutin of borane-tetrahydrofuran complex in tetrahydrofuran(8.9ml) was added dropwise to a stirred solution of(S)-2,3,4,5-tetrahydro-1-benzoxepine -4-carboxylic acid(860mg) in tetrahydrofuran(4.5ml) in an atmosphere of nitrogen under ice cooling over 20 minutes. The resulting mixture was stirred under the same conditions for 2 hours and allowed to stand at room temperature overnight. Water was added dropwise to the stirred reaction mixture under ice cooling and the mixture was extracted with methylene chloride. The extract was washed with a

saturated sodium bicarbonate aqueous solution, dried over sodium sulfate, and evaporated in vacuo to afford (S)-(2,3,4,5-tetrahydro-1-benzoxepin-4-yl)methanol (0.82g) as a crude solid.

IR(Nujol); 3200, 1220cm^{-1}.

^{1}HNMR($CDCl_3$) δ; 1.58(1H, s), 1.69-1.91(2H, m), 1.95-2.05(1H, m), 2.68-2.89(2H, m), 3.63(2H, d, J=9.7Hz), 3.68-3.81(1H, m), 4.30-4.42(1H, m), 6.93-7.02(2H, m), 7.09-7.18(2H, m).

(+)APCI MS m/z; 161(M^+-OH).

Preparation 56

A solution of triethylamine(630mg) in methylene chloride(2.5ml) was added dropwise to a solution of(S)-(2,3,4,5-tetrahydro-1-benzoxepin-4-yl)methanol(0.74g) and methanesulfonyl chloride(571mg) in methylene chloride(7.5ml) under ice cooling over 10 minutes and the mixture was stirred at the same temperature for 4 hours. The reaction mixture was treated with 1N hydrochloric acid and extracted with methylene chloride. The extract was washed successively with brine, a saturated sodium bicarbonate aqueous solution, and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was chromatographed(toluene-ethyl acetate) over silica gel to afford (S)-2,3,4,5-tetrahydro-1-benzoxepin-4-yl methanesulfonate(1.02g) as an pale yellow oil.

$[\alpha]_D^{23}$-44.1° (c=0.615, CH_2Cl_2).

IR(Nujol); 1345, 1220, 1165cm^{-1}.

^{1}HNMR($CDCl_3$) δ; 1.82-2.18(3H, m), 2.80-2.85(2H, m), 3.02(3H, s), 3.72(1H, m), 4.15(2H, d, J=6.8Hz), 4.27-4.38(1H, m), 6.95-7.03(2H, m), 7.12-7.23(2H, m).

(+)APCI MS m/z; 257(M^++1), 161(M^+-OMs).

Preparation 57

Acetaminomalonic acid diethyl ester(2.49g) was added to a solution of sodium(262mg) in ethanol(6.7ml) and a solution of(S)-2,3,4,5-tetrahydro-1-benzoxepin-4-yl methanesulfonate(978mg) in tetrahydrofuran(5.5ml) was added dropwise thereto with stirring at room temperature. The resulting mixture was stirred under reflux for 22 hours, cooled to room temperature, and evaporated in vacuo. The residue was partitioned between ethyl acetate and water. The organic

layer was saparated, washed with brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was chromatographed(toluene-ethyl acetate) over silica gel to afford 2-acetylamino-2-[2-(R)-2, 3, 4, 5-tetrahydro-1-benzoxepin-4-yl)methyl] malonic acid diethyl ester(436mg) as an oil.

$[\alpha]_D^{22}$-6.5° (c=0.585, CH_2Cl_2).

IR(film); 3370(br), 3300(br), 1740(br), 1670(br)cm^{-1}.

^{1}HNMR($CDCl_3$) δ ; 1.21-1.34(6H, m), 1.62-1.84(3H, m), 2.04(3H, s), 2.33-2.78(4H, m), 3.65-3.76(1H, m), 4.14-4.33(5H, m), 6.85-7.30(5H, m).

(+)APCI MS m/z; 378(M^++1).

Preparation 58

A solution of 2-acetylamino-2-[2-((R)-2, 3, 4, 5-tetrahydro-1-benzoxepin-4-yl)methel]malonic acid diethyl ester(420mg) and potassium hydroxide(125mg) in ethanol(2.1ml) and water(2.1ml) was refluxed for 4 hours and cooled to room temperature. The reaction mixture was acidified with hydrochloric acid and extracted with ethyl acetate. The extract was washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo to afford 2-acetylamino-3-((R)-2, 3, 4, 5-tetrahydro-1-benzoxepin-4-yl)propionic acid(217mg) as a crude oil.

IR(film); 3300(br), 1720(br), 1655-1615(br), 1225(br)cm^{-1}.

^{1}HNMR($CDCl_3$) δ ; 1.60-2.15(5H, m), 2.03(3H, s), 2.65-2.85(2H, m), 3.79(1H, m), 4.25(1H, m), 4.63-4.77(1H, m), 5.11(1H, br), 6.12-6.24(1H, m), 6.93-7.01(2H, m), 7.08-7.18(2H, m).

(+)APCI MS m/z; 278(M^++1).

Preparation 59

A mixture of 2-acetylamino-3-((R)-2, 3, 4, 5-tetrahydro-1-benzoxepin-4-yl) propionic acid(201mg) and 1N hydrochloric acid(2.0ml) was stirred under reflux and cooled to room temperature. The reaction mixture was evaporated in vacuo. The powdery residue was washed with diethyl ether to afford 2-amino-3-((R)-2, 3, 4, 5-tetrahydro-1-benzoxepin-4-yl)propionic acid hydrochloride(160mg) as a colorless powder; mp191-205℃(dec.).

$[\alpha]_D^{21}$-22.2° (c=0.55, MeOH).

IR(Nujol); 2600(br), 1755, 1745, 1730cm^{-1}.

^{1}HNMR(D_6-DMSO) δ; 1.62-2.05(5H, m), 2.61-2.84(2H, m), 3.63-3.80(1H, m), 3.95(1H, m), 4.13-4.26(1H, m), 6.89-7.01(2H, m), 7.10-7.24(2H, m), 8.41(3H, br).
(+)APCI MS m/z; 236(M^++1).

Preparation 60

A solution of di-tert-butyl dicarbonate(140mg) in acetone(0.5ml) was added dropwise to a stirred solution of 2-amino-3-((R)-2,3,4,5-tetrahydro-1-benzoxepin-4-yl)propionic acid hydrochloride(134mg) and triethylamine(150mg) in acetone(1.5ml) and water(1.5ml) under ice cooling, and the resulting mixture was stirred at room temperature for 15 hours. The reaction mixture was evaporated in vacuo, and then the residue was diluted with water(5ml)-0.1N hydrochloric acid (10ml) and extracted with ethyl acetate. The extract was washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo to afford 2-tert-butoxycarbonylamino-3-((R)-2,3,4,5-tetrahydro-1-benzoxepin-4-yl)propionic acid (168mg) as a colorless amorphous powder.
IR(film); 2320, 2550, 1700, 1225cm^{-1}.
^{1}HMNR($CDCl_3$) δ; 1.43 and 1.44(9H, each s), 1.57-2.15(5H, m), 2.65-2.85(2H, m)3.65-3.85(1H, m), 4.25(1H, m), 4.45(1H, m), 4.89(1H, m), 5.91(1H, br), 6.93-7.01(2H, m), 7.09-7.18(2H, m).

Preparation 61

1-Ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride(120mg) was added to a mixture of 2-tert-butoxycarbonylamino-3-((R)-2,3,4,5-tetrahydro-1-benzoxepin-4-yl)propionic acid(151mg), 1-methanesulfonylspiro[indoline-3,4'-piperidine]hydrochloride(126mg), N-methylmorpholine(63mg), and 1-hydroxybenzotriazole(62mg) in dichloromethane(3.9ml) at room temperature, and the resulting mixture was stirred at the same temperature overnight. The reaction mixture was washed successively with water, 0.1N hydrochloric acid, water, a saturated sodium bicarbonate aqueous solution, and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was chromatographed(n-hexame-ethyl acetate) over silica gel to afford 1'-[2-tert-butoxycarbonylamino-3-((R)-2,3,4,5-tetrahydro-1-benzoxepin-4-yl)propionyl]-1-methanesulfonylspiro[indoline-3,4'-piperidine](200mg) as a colorless powder; mp88-90℃.

IR(Nujol); 3370, 3280, 1690, 1630, 1340, 1155cm^{-1}.
^{1}HNMR(CDCl) δ; 1.40, 1.42 and 1.45(9H, each s), 1.35-2.25(9H, m), 2.60-3.30(4H, m), 2.92(3H, s), 3.60-4.35(5H, m), 4.62(1H, m), 4.81(1H, m), 5.31(1H, m), 6.90-7.30(7H, m), 7.41(1H, d, J=8.0Hz).
(+)APCI MS m/z; 584(M+1), 484(M-Boc+2).

Preparation 62

A mixture of 1'-[2-tert-butoxycarbonylamino-3-((R)-2,3,4,5-tetrahydro-1-benzoxepin-4-yl)propionyl]-1-methanesulfonylspiro[indoline-3,4'-piperidine] (159mg) and 4N hydrogenchloride in ethyl acetate(3.2ml) was stirred under ice cooling for 1 hour and at room temperature for 2 hours and evaporated in vacuo. The residue was partitioned between ethyl acetate and a saturated sodium bicarbonate aqueous solution. The organic layer was separated, washed with brine, dried over sodium sulfate, and evaporated in vacuo to afford 1'-[2-amino-3-((R)-2,3,4,5- tetrahydro-1-benzoxepin-4-yl)propionyl]-1-methanesulfonylspiro[indoline-3,4'-piperidine](126mg) as a colorless powder; mp75.5-99℃.
IR(Nujol); 3350(br), 1620, 1340, 1215, 1155cm^{-1}.
^{1}HNMR($CDCl_3$) δ; 1.20-2.30(9H, m), 2.60-3.30(4H, m), 2.92 and 2.93(3H, each s), 3.48 and 3.75-4.35(6H, each m), 4.65(1H, m), 6.96-7.30(7H, m), 7.40(1H, d, J=8.0Hz).
(+)APCI MS m z; 484(M$^+$+1).

Preparation 63

A mixture of 2,3,4,5-tetrahydro-5-oxo-1-benzoxepine-4-carboxylic acid ethyl ester(468mg), [(S)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl]ruthenium (II)chloride, triethylamine complex(1:1)(8.4mg), D-camphorsulfonic acid(9.3mg), and methylene chloride(10ml) was heated in the presence of hydrogen at a pressure of 90atm at 50℃ for 90 hours. The reaction mixture was worked up in a usual manner to afford(4S, 5R)-2,3,4,5-tetrahydro-5-hydroxy-1-benzoxepine-4-carboxylic acid ethyl ester(256mg) as a powder; mp67-69.5℃.
IR(Nujol); 3480, 1720, 1225cm^{-1}.
^{1}HNMR($CDCl_3$) δ; 1.26(3H, t, J=7.1Hz), 2.20-2.30(2H, m), 2.80-2.91(1H, m), 3.04 (1H, br s), 3.79-3.91(1H, m), 4.17(2H, d, J=7.1Hz), 4.22-4.33(1H, m), 5.18(1H, d,

J=8.5Hz), 7.0(1H, dd, J=7.7, 1.5Hz), 7.07-7.27(2H, m), 7.51(1H, dd, J=7.3, 1.4Hz).
(+)APCI MS m/z; 219(M^+-OH).

Preparation 64

Acetic anhydride(84mg)was added dropwise to a stirred solution of(4S,5R)-2,3,4,5-tetrahydro-5-hydroxy-1-benzoxepine-4-carboxylic acid ethyl ester(130mg), 4-dimethylaminopyridine(1mg), and pyridine(65mg) in tetrahydrofuran(1.3ml)under ice cooling and the resulting mixture was stirred at the same temperature for 21 hours. The reaction mixture was extracted with ethyl acetate and the extract was washed successively with 1N hydrochloric acid, water, saturated sodium bicarbonate aqueous solution, and brine, dried over magnesium sulfate, and evaporated in vacuo to afford(4S, 5R)-5-acetoxy-2,3,4,5-tetrahydro-1-benzoxepine-4-carboxylic acid ethyl ester(145mg) as a colorless oil.
IR(film); 1745, 1720cm^{-1}.
^{1}HNMR($CDCl_3$) δ; 1.20(3H, t, J=7.1Hz), 2.11(3H, s), 2.25-2.36(2H, m), 3.04-3.15(1H, m), 3.98-4.23(4H, m), 6.32(1H, d, J=7.6Hz), 6.98-7.09(2H, m), 7.18-7.29(2H, m).
(+)APCI MS m/z; 219(M^+-OAc).

Preparation 65

A mixture of(4S, 5R)-5-acetoxy-2,3,4,5-tetrahydro-1-benzoxepine-4-carboxylic acid ethyl ester(122mg) and 10% Pd/C(120mg) in ethyl acetate(4ml) was stirred in the presence of hydrogen at 4.6atm at room temperature for 17 hours and filtered. The filtrate was evaporated in vacuo and the residue(108mg) was chromatographed(toluene-ethyl acetate) over silica gel(2.2g) to afford (4R)-2,3,4,5-tetrahydro-1-benzoxepine-4-carboxylic acid ethyl ester(76mg) as a colorless oil.
IR(film); 1730, 1225cm^{-1}.
^{1}HNMR($CDCl_3$) δ; 1.26(3H, t, J=7.1Hz), 2.13-2.25(2H, m), 2.59-2.68(1H, m), 3.00(1H, dd, J=14.2, 2.6Hz), 3.14(1H, dd, J=14.2, 9.5Hz), 3.75-3.88(1H, m), 4.14(2H, q, J=7.1Hz), 4.25-4.37(1H, m), 6.94-7.03(2H, m), 7.10-7.19(2H, m).
(+)APCI MS m/z; 221(M^++1), 175(M^+-OEt).

Preparation 66

A solution of(4R)-2, 3, 4, 5-tetrahydro-1-benzoxepine-4-carboxylic acid ethyl ester(66mg) and lithium hydroxide(14mg) in ethanol(0.7ml), tetrahydrofuran (0.7ml), and water(0.86ml) was stirred at room temperature for 50 minutes, and then the reaction mixture was extracted with saturated sodium bicarbonate aqueous solution. The extracted aqueous solution was washed with diethyl ether, acidified with 1N hydrochloric acid, and extracted twice with ethyl acetate. The extract was dried over sodium sulfate and evaporated in vacuo to afford (4R)-2, 3, 4, 5-tetrahydro-1-benzoxepine-4-carboxylic acid(59mg) as a colorless powder; mp95.5-98℃.

$[\alpha]_D^{19}$+77.1° (c=0.87, CH_2Cl_2).

IR(film): 1730, 1690, 1250, 1220cm^{-1}.

^{1}HNMR($CDCl_3$) δ; 2.04-2.30(2H, m), 2.64-2.78(1H, m), 2.99-3.22(2H, m), 3.75-3.88 (1H, m), 4.26-4.37(1H, m), 6.96-7.05(2H, m), 7.12-7.21(2H, m).

Example 1

1-Ethyl-3-(3'-dimethylaminopropyl)carbodiimide (89 mg) was added to a mixture of 2-[[2-(tert-butoxycarbonylamino)-2, 2-dimethyl-1-oxoethyl]amino]-3-(2, 3-dihydro-1-benzoxepin-4-yl)propionic acid (200 mg) 1-methanesulfonylspiro-[indoline-3, 4'-piperidine]hydrochloride (145 mg), and 1-hydroxybenzotriazole (78 mg) in N, N-dimethylformamide (4 ml) at ambient temperature and the resulting mixture was stirred at the same temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with water (twice) and brine, dried over sodium sulfate, and evaporated in vacuo. The reside was chromatographed (n-hexane - ethyl acetate) over silica gel to afford N-[1-[(1-methanesulfonylspiro[indoline-3, 4'-piperidine]-1'-yl) carbonyl]-2-(2, 3-dihydro-1-benzoxepin-4-yl)ethyl]-2-[(tert-butoxycarbonyl)amino] -2-methylpropanamide (255 mg) as a pale yellow foam.

IR(film): 3380, 3280, 1700, 1625, 1340, 1155 cm^{-1}.

^{1}H NMR($CDCl_3$) δ: 1.37(3H, s), 1.45(9H, s), 1.46(3H, s), 1.6 - 1.8(4H, m), 2.57 - 2.76(5H, m), 2.88 and 2.90(3H, each s), 3.20(1H, m), 3.76 - 4.18(4H, m), 4.28 and 4.57 (2H, m), 4.86(1H, br s), 5.17(1H, m), 6.17 and 6.24(1H, each s), 6.81 - 7.42(8H, m).

(+)APCI MS m/z: 667(M^+ + 1), 567.

Example 2

A suspension of N-[1-[(1-methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl)carbonyl]-2-(2,3-dihydro-1-benzoxepin-4-yl)ethyl]-2-[(tert-butoxycarbonyl)amino]-2-methylpropanamide (100 mg) in 4 N hydrogenchloride in ethyl acetate (2 ml), ethyl acetate (5 ml), and methanol (1 ml) was stirred at ambient temperature for 9 hours and evaporated in vacuo. The residue was powdered from ethyl acetate and the powder was washed with diethyl ether to afford N-[1-[(1-methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl)carbonyl]-2-(2,3-dihydro-1-benzoxepin-4-yl)ethyl]-2-amino-2-methylpropanamide hydrochloride (80 mg) as a pale yellow powder: mp 175℃.

IR(film): 3350, 3210, 2750 - 2500, 1670, 1625, 1345, 1160 cm^{-1}.

^1H NMR(CD_3OD) δ: 1.45 and 1.49(3H, each s), 1.58 and 1.61(3H, each s), 1.79(4H, m), 2.6 - 2.8(5H, m), 2.95 and 2.97(3H, each s), 3.91(2H, m), 4.07 - 4.21(4H, m), 4.5 (1H, m), 4.86(1H, br s), 5.19(1H, m), 6.24 and 6.28(1H, each s), 6.88 - 7.36(8H, m).

Example 3

A mixture of N-[1-[(1-methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl)carbonyl]-2-(2,3-dihydro-1-benzoxepin-4-yl)ethyl]-2-[(tert-butoxycarbonyl)amino]-2-methylpropanamide (130 mg) and 10 % Pd/C (a catalytic amount) in ethyl acetate (5 ml), methanol (5 ml) and acetone (5 ml) was stirred in the presence of an atmospheric hydrogen at ambient temperature for 8 hours and filtered. The filtrate was evaporated in vacuo to afford N-[1-[(1-methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl)carbonyl]-2-(2,3,4,5-tetrahydro-1-benzoxepin-4-yl)ethyl]-2-[(tert-butoxycarbonyl)amino]-2-methylpropanamide (132 mg) as a colorless foam.

IR(film): 3380, 3300, 1700, 1635, 1340, 1155 cm^{-1}.

^1H NMR($CDCl_3$) δ: 1.38 - 2.2(24H, m), 2.65 - 2.85(2H, m), 2.92(3H, s), 2.85 - 5.15 (9H, m), 6.93 - 7.42(8H, m).

(+)APCI MS m z: 669(M^+ + 1).

Example 4

A mixture of N-[1-[(1-methanesulfonylspiro[indoline-3,4'-piperidine]-1'

-yl)carbonyl]-2-(2, 3, 4, 5-tetrahydro-1-benzoxepin-4-yl)ethyl]-2-[(tert-butoxycarbonyl)amino]-2-methylpropanamide (122 mg) 4 N hydrogenchloride in ethyl acetate (1 ml), and ethyl acetate (3 ml) was stirred at ambient temperature overnight and evaporated in vacuo. The residue was washed with diethyl ether to afford 2-amino-N-[1-[(1-methanesulfonylspiro[indoline-3, 4'-piperidine]-1'-yl) carbonyl]-2-(2, 3, 4, 5-tetrahydro-1-benzoxepin-4-yl)ethyl]-2-methylpropanamide hydrochloride (94 mg) as a colorless powder.

m.p. 160℃.

IR(film): 3370, 3250, 2930 - 2570, 1670, 1625, 1345, 1155 cm^{-1}.

^1H NMR(CD_3OD) δ: 1.5 - 2.2(15H, m), 2.77(2H, m), 2.97 - 3.00(3H, m), 3.1 - 4.6(8H, m), 5.04(1H, m), 6.88 - 7.40(8H, m).

(+)APCI MS m/z: 569(M^+ + 1).

Example 5

N-[1-[(4-Cyano-4-phenylpiperidinyl)carbonyl]-2-(2, 3-dihydro-1-benzoxepin-4-yl)ethyl]-2-[(tert-butoxycarbonyl)amino]-2-methylpropanamide was prepared from 2-[[2-(tert-butoxycarbonylamino)-2, 2-dimethyl-1-oxoethyl]amino]-3-(2, 3-dihydro-1-benzoxepin-4-yl)propionic acid and 4-cyano-4-phenylpiperidine hydrochloride in a similar manner to Example 1.

A colorless powder: mp 84-89℃(from n-hexane).

IR(film): 3400, 3280, 1700, 1635cm^{-1}.

^1H NMR($CDCl_3$) δ: 1.40(6H, s), 1.45(9H, s), 1.65-2.25(4H, m), 2.55-2.8(3H, m), 3.0-3.15 (1H, m), 3.45-3.65(1H, m), 4.05-4.35(3H, m), 4.7-4.85(2H, m), 5.14-5.22(1H, m), 6.18 and 6.21(1H, each s), 6.85-7.56(11H, m).

(+)APCI MS m/z : 587(M^++1), 531, 487.

Example 6

2-Amino-N-[1-[(4-cyano-4-phenylpiperidinyl)carbonyl]-2-(2, 3-dihydro-1-benzoxepin-4-yl)ethyl]-2-methylpropanamide hydrochloride was prepared from N-[1-[(4-cyano-4-phenylpiperidinyl)carbonyl]-2-(2, 3-dihydro-1-benzoxepin-4-yl)ethyl]-2-[(tert-butoxycarbonyl)amino]-2-methylpropanamide in a similar manner to Example 4.

A colorless powder: mp 154-168℃(dec.)(from diethyl ether).

IR(film): 3400-3100, 2730, 2550, 2200, 1660, 1620cm^{-1}.

^{1}H NMR(CD_3OD) δ: 1.43 and 1.49(3H, each s), 1.58(3H, s), 1.65-2.25(4H, m), 2.55-2.8 (3H, m), 2.95-3.15(1H, m), 3.45-3.65(1H, m), 4.1-4.35(3H, m), 4.65-4.8(1H, m), 5.15-5.25 (1H, m), 6.25(1H, s), 6.81-6.97(2H, m), 7.03-7.16(2H, m), 7.30-7.51(5H, m).

(+)APCI MS m/z : 487(M^++1).

Example 7

2-Amino-N-[1-[(4-cyano-4-phenylpiperidyl)carbonyl]-2-(2, 3, 4, 5-tetrahydro -1-benzoxepin-4-yl)ethyl]-2-methylpropanamide hydrochloride was prepared from 2-amino-N-[1-[(4-cyano-4-phenylpiperidyl)carbonyl]-2-(2, 3-dihydro-1-benzoxepin-4-yl)ethyl]-2-methylpropanamide hydrochloride in a similar manner to Example 3.

A colorless powder: mp 139-150℃.

IR(film): 3380-3200, 2650, 2560, 2520, 2230, 1660, 1625, 1220cm^{-1}.

^{1}H NMR(CD_3OD) δ: 1.55, 1.58, 1.59, and 1.62(6H, each s), 1.7-2.25(9H, m), 2.7-3.15 (3H, m), 3.4-4.0(1H, m), 4.1-4.75(4H, m), 4.95-5.1(1H, m), 6.85-7.25(4H, m), 7.4-7.55(5H, m).

(+)APCI MS m/z : 489(M^++1).

Example 8

1-Ethyl-3-(3'-dimethylaminopropyl)carbodimide hydrochloride(179mg) was added to a mixture of 1'-[(2R)-2-amino-3-[(4S)-2, 3, 4, 5-tetrahydro-1-benzoxepin-4 -yl]propionyl]-1-methanesulfonylspiro[indoline-3, 4'-piperidine](300ml), N-tert-butoxycarbonyl-α-methylalanine(145mg) and 1-hydroxybenzotriazole(101mg) in dichloromethane(20ml) at 5℃ with stirring. After stirring for 4 hours at 5℃, the reaction mixture was evaporated, and the residue was partitioned between ethyl acetate and water. The organic layer was separated, washed in turn with 0.1N aqueous hydrochloric acid, brine, saturated sodium hydrogen carbonate in water and brine(twice), and dried over magnesium sulfate. Evaporation of the solvent gave a residue, which was chromatographed on silica gel eluting with a mixture of toluene and ethyl acetate(5:1, 3:1, 1:1 and 1:2(v/v) successively) to give N-[(1R)-1-[(1-methanesulfonylspiro[indoline-3, 4'-piperidine]-1'-yl)carbonyl]-2-[(4S)-2, 3, 4, 5-tetrahydro-1-benzoxepin-4-yl]ethyl]-2-[(tert-butoxycarbonyl)amino] -2-methylpropanamide(290mg) as a foam.

FT IR(film);1712.5, 1639.2, 1488.8, 1452.1cm^{-1}
NMR($CDCl_3$)(mixture of rotamers) δ;1.38(9H, s), 1.42-1.48(6H, m), 1.60-2.35(9H, m), 2.60-2.90(3H, m), 2.92(3H, s), 3.05-3.35(1H, m), 3.70-4.35(5H, m), 4.45-4.70 (1H, m), 4.85(1H, s), 4.95-5.10(1H, m), 6.90-7.45(8H, m)
(+)FAB MS m/z; 569(M^+-CO_2Bu^t+1), 669.1(M^++1)

Example 9

To a solution of N-[(1R)-1-[(1-methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl)carbonyl]-2-[(4S)-2,3,4,5-tetrahydro-1-benzoxepin-4-yl]ethyl]-2-[(tert-butoxycarbonyl)amino]-2-methylpropanamide(260mg) in ethyl acetate(4ml) was added 4N hydrochloric acid in ethyl acetate(4ml), which was stirred for 2 hours at ambient temperature. The reaction mixture was evaporated and azeotroped three times with ethyl acetate to give powder. The powder was collected, washed with ethyl ether and dried in vacuo to give N-[(1R)-1-[(1-methanesulfonylspiro-[indoline-3,4'-piperidine]-1'-yl)carbonyl]-2-[(4S)-2,3,4,5-tetrahydro-1-benzoxepin-4-yl]ethyl]-2-amino-2-methylpropanamide hydrochloride(210mg).
FT IR(KBr);1670.0, 1631.5, 1527.3, 1481.1, 1461.8cm^{-1}
NMR(CD_3OD)(mixture of rotamers) δ;1.50-2.20(15H, m), 2.60-3.00(6H, m), 3.10-3.55 (1H, m), 3.60-4.60(6H, m), 4.90-5.10(1H, m), 6.88-7.40(8H, m)
(+)FAB MS m/z; 569(M^++1)
Analysis: Calculated for $C_{30}H_{41}ClN_4O_5S \cdot 5/2H_2O$;
C, 55.42; H, 7.13; N, 8.62
Found:C, 55.46; H, 7.04; N, 8.58

Example 10

N-[(1R)-1-[(1-Methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl)-carbonyl]-2-[(4R)-2,3,4,5-tetrahydro-1-benzoxepin-4-yl]ethyl]-2-[(tert-butoxycarbonyl)amino]-2-methylpropanamide was prepared according to a similar manner to that of Example 8 as a foam.
FT IR(film);1712.5, 1639.2, 1488.8, 1452.4, 1349.9cm^{-1}
NMR($CDCl_3$)(mixture of rotamers) δ;1.42-2.40(24H, m), 2.55-3.20(4H, m), 2,92(3H, s), 3.50-4.20(5H, m), 4.40-4.60(1H, m), 4,90(1H, br-s), 5.00-5.20(1H, m), 6.85-7.45(8H, m)

(+)FAB MS m/z; 569($M^+-CO_2Bu^t+1$), 669(M^++1)

Example 11

N-[(1R)-1-[(1-Methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl)-carbonyl]-2-[(4R)-2,3,4,5-tetrahydro-1-benzoxepin-4-yl]ethyl]-2-amino-2-methylpropanamide hydrochloride was prepared according to a similar manner to that of Example 9 as a white powder.

FT IR(KBr);1670.0, 1631.5, 1529.3, 1481.1, 1459.8cm^{-1}

NMR(CD_3OD)(mixture of rotamers) δ;1.50-2.20(15H, m), 2.60-3.40(7H, m), 3.60-4.60 (6H, m), 5.00-5.20(1H, m), 6.88-7.40(8H, m).

(+)FAB MS m/z;569(M^++1)

Analysis. Calculated for $C_{30}H_{41}ClN_4O_5S \cdot 11/4H_2O$:

C, 55.03;H, 7.16; N, 8.56.

Found: C, 54.91; H, 7.04;N, 8.54.

Example 12

N-[(1S)-1-[(1-Methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl)-carbonyl]-2-[(4R)-2,3,4,5-tetrahydro-1-benzoxepin-4-yl]ethyl]-2-[(tert-butoxycarbonyl)amino]-2-methylpropanamide was prepared according to a similar manner to that of Example 8 as a foam.

FT IR(film);1714.4, 1639.2, 1488.8, 1454.1cm^{-1}

NMR($CDCl_3$)(mixture of rotameres) δ; 1.38(9H, s), 1.42-1.48(6H, m), 1.60-2.35(9H, m), 2.60-2.90(3H, m), 2.92(3H, s), 3.05-3.35(1H, m), 3.70-4.35(5H, m), 4.45-4.70H, m), 4.85(1H, m), 4.95-5.10(1H, m), 6.90-7.45(8H, m).

(+)FAB MS m/z;569($M^+-CO_2Bu^t$+1), 669(M^++1)

Example 13

N-[(1S)-1-[(1-Methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl)-carbonyl]-2-[(4R)-2,3,4,5-tetrahydro-1-benzoxepin-4-yl]ethyl]-2-amino-2-methylpropanamide hydrochloride was prepared according to a similar manner to that of Example 9 as a white powder.

FT IR(KBr);1672.0, 1633.4, 1525.4, 1481.1, 1457.9cm^{-1}

NMR(CD_3OD)(mixture of rotamers) δ; 1.50-2.20(15H, m), 2.60-3.00(6H, m), 3.10-3.55

(1H, m), 3.60-4.60(6H, m), 4.90-5.10(1H, m), 6.88-7.40(8H, m).
(+)FAB MS m/z;569(M$^+$+1)
Analysis:Calculated for $C_{30}H_{41}ClN_4O_5S \cdot 9/8H_2O$,
C, 57.61; H, 6.97; N, 8.96
Found: C, 57.86 ; H, 7.18 ; N, 8.62

Example 14

N-[(1S)-1-[(1-Methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl)-carbonyl]-2-[(4S)-2,3,4,5-tetrahydro-1-benzoxepin-4-yl]ethyl]-2-[(tert-butoxycarbonyl)amino]-2-methylpropanamide was prepared according to a similar manner to that of Example 8 as a foam.
FT IR(film);1712.5, 1639.2, 1488.8, 1454.1cm^{-1}
NMR($CDCl_3$)(mixture of rotamers) δ ; 1.42-2.40(24H, m), 2.55-3.20(4H, m), 2.92(3H, s), 3.50-4.20(5H, m), 4.40-4.60(1H, m), 4.90(1H, s), 5.00-5.20(1H, m), 6.85-7.45 (8H, m).
(+)FAB MS m/z;569(M$^+$-CO_2Bu^t+1), 669(M$^+$+1)

Example 15

N-[(1S)-1-[(1-Methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl)-carbonyl]-2-[(4S)-2,3,4,5-tetrahydro-1-benzoxepin-4-yl]ethyl]-2-amino-2-methylpropanamide hydrochloride was prepared according to a similar manner to that of Example 9 as a white powder.
FT IR(KBr);1672.0, 1631.5, 1527.3, 1483.0, 1459.8cm^{-1}
NMR(CD_3OD)(mixture of rotamers) δ ; 1.50-2.20(15H, m), 2.60-3.40(7H, m), 3.60-4.60 (6H, m), 5.00-5.20(1H, m), 6.88-7.40(8H, m).
(+)FAB MS m/z;569(M$^+$+1)
Analysis: Calculated for $C_{30}H_{41}ClN_4O_5S \cdot 23/16H_2O$,
C, 57.10; H, 7.00; N, 8.80
Found: C, 57.52; H, 7.10; N, 8.39

Example 16

N-[(1R)-1-[(1-Methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl) carbonyl]-2-(2,3-dihydro-1-benzoxepin-4-yl)ethyl]-2-[(tert-butoxycarbonyl)amino] -2-methylpropanamide was prepared according to the similar manner as that of Example 8 as a foam.

FT IR(film): 1714.4, 1639.2, 1488.8, 1454.1cm^{-1}.

NMR($CDCl_3$)(mixture of rotamers) δ: 1.35-2.40(19H, m), 2.45-2.85(5H, m), 2.88 and 2.90(3H(1:1), 2×s), 3.10-3.30(1H, m), 3.70-3.90(2H, m), 3.95-4.40(3H, m), 4.50-4.70(1H, m), 4.86(1H, s), 5.05-5.25(1H, m), 6.17 and 6.24(1H(1:1), 2×s), 6.36, 6.40 and 6.85-7.42(8H, m).

(+)FAB MS m/z: 567($M^+-CO_2Bu^t+1$), 667(M^++1).

Example 17

N-[(1R)-1-[(1-Methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl) carbonyl]-2-(2,3-dihydro-1-benzoxepin-4-yl)ethyl]-2-amino-2-methylpropanamide hydrochloride was prepared according to the similar manner as that of Example 9 as a white powder.

FT IR(KBr): 1672.0, 1631.5, 1523.5, 1481.1cm^{-1}.

NMR(CD_3OD)(mixture of rotamer) δ: 1.42-2.01(10H, m), 2.50-3.00(8H, m), 3.10-3.50 (1H, m), 3.80-4.30(5H, m), 4.40-4.60(1H, m), 5.10-5.30(1H, m), 6.24 and 6.28(1H (1:1), 2×S), 6.65-7.40(8H, m).

(+)FAB MS m/z: 567(M^++1).

$[\alpha]_D^{20.0}$+13.8° (c=0.5, MeOH).

Anal: Calcd for $C_{30}H_{39}ClN_4O_5S \cdot 1\frac{1}{2}H_2O$, C, 57.18; H, 6.72; N, 8.89. Found:C, 57.20; H, 6.83; N, 8.53.

Example 18

N-[(1S)-1-[(1-Methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl)carbonyl]-2-(2,3-dihydro-1-benzoxepin-4-yl)ethyl]-2-[(tert-butoxycarbonyl)amino-2-methylpropanamide was prepared according to the similar manner as that of Example 8 as a foam.

FT IR(film); 1716.3, 1639.2, 1567.8, 1488.8, 1452.1cm^{-1}.

NMR($CDCl_3$)(mixture of rotamers) δ; 1.35-2.40(19H, m), 2.45-2.85(5H, m), 2.88 and 2.90(3H(1:1), 2×s), 3.10-3.30(1H, m), 3.70-3.90(2H, m), 3.95-4.40(3H, m), 4.50-4.70(1H, m), 4.86(1H, s), 5.05-5.25(1H, m), 6.17 and 6.24(1H(1:1), 2×S), 6.36, 6.40 and 6.85-7.42(8H, m),

(+)FAB MS m/z; 567(M^+-CO_2Bu^t+1), 667(M^++1).

Example 19

N-[(1S)-1-[(1-Methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl)carbonyl]-2-(2,3-dihydro-1-benzoxepin-4-yl)ethyl]-2-amino-2-methylpropanamide hydrochloride was prepared according to the similar manner as that of Example 9 as a white powder.

FT IR(KBr); 1673.9, 1631.5, 1523.5, 1481.1cm^{-1}.

NMR(CD_3OD)(mixture of rotamers) δ; 1.42-2.01(10H, m), 2.50-3.00(8H, m), 3.10-3.50(1H, m), 3.80-4.30(5H, m), 4.40-4.60(1H, m), 5.10-5.30(1H, m), 6.24 and 6.28(1H(1:1), 2×s), 6.65-7.40(8H, m).

(+)FAB MS m/z; 567(M^++1).

$[\alpha]_D^{20.0}$-12.2° (C=0.5, MeOH)

Anal: Calcd for $C_{30}H_{39}ClN_4O_5S \cdot 1\frac{1}{2}H_2O$,

C, 57.18; H, 6.72; N, 8.89. Found: C, 57.17; H, 6.82; N, 8.49.

Example 20

Ethyl 3-benzyl-1-[(2R)-2-[(2-tert-butoxycarbonyl)amino]-2-methylpropionylamino)]-3-(2,3-dihydro-1-benzoxepin-4-yl)propionyl]piperidine-3-carboxylate was prepared according to a similar manner to that of Example 8 as a foam.

FT IR(KBr); 1720.2, 1673.9, 1643.1, 1490.7, 1454.1, 1444.4cm^{-1}.

NMR($CDCl_3$)(mixture of rotamers) δ; 1.05-1.80(22H, m), 2.00-3.70(8H, m), 3.90-5.30

(8H, m), 6.05-6.20(1H, m), 6.80-7.30(9H, m).
(+)APCI MS m/z; 592(M^+-C(CH_3)$_3$+2), 648(M^++2).

Example 21

Ethyl 3-benzyl-1-[(2R)-2-[(2-tert-butoxycarbonyl)amino]-2-methylpropionylamino)]-3-(2,3-dihydro-1-benzoxepin-4-yl)propionyl]piperidine-3-carboxylate(280mg) was dissolved in methanol(30ml), and 10% palladium on carbon (50mg) was added. The resulting mixture was stirred at ambient temperature under hydrogen atmosphere. After 5 hours, the catalyst was removed by filtration, and the filtrate was cancentrated in vacuo to give ethyl 3-benzyl-1-{(2R)-2-[(2-tert-butoxycarbonyl)amino]-2-methylpropionylamino)}-3-(2,3,4,5-tetrahydro-1-benzoxepin-4-yl)propionyl]piperidine-3-carboxylate(270mg) as a foam.
FT IR(KBr); 1720.2, 1673.9, 1643.1, 1490.7, 1454.1cm^{-1}.
NMR($CDCl_3$)(mixture of rotamers) δ; 1.05-2.20(27H, m), 2.30-5.40(14H, m), 6.80-7.40(9H, m).
(+)APCI MS m/z; 594(M^+-C(CH_3)$_3$+2), 650(M^++1).

Example 22

Ethyl 1-[(2R)-2-(2-amino-2-methylpropionylamino)-3-(2,3-dihydro-1-benzoxepin-4-yl)propionyl]-3-benzylpiperidine-3-carboxylate hydrochloride was prepared according to a similar manner to that of Example 9 as a white powder.
FT IR(KBr); 1724.1, 1675.8, 1633.4, 1569.8, 1544.7, 1517.7, 1490.7, 1454.1, 1444.4cm^{-1}.
NMR(CD_3OD)(mixture of rotamers) δ; 1.10-3.40(21H, m), 3.60-5.40(7H, m), 6.05-6.30(1H, m), 6.80-7.40(10H, m).
(+)APCI MS m/z; 548(M^++1).
Anal: Calcd for $C_{32}H_{42}ClN_3O_5 \cdot 1\frac{1}{2}H_2O$: C, 62.89; H, 7.42; N, 6.88. Found:C, 62.96; H, 7.45; N, 6.73.

Example 23

Ethyl 1-[(2R)-2-(2-amino-2-methylpropionylamino)-3-(2, 3, 4, 5-tetrahydro-1-benzoxepin-4-yl)propionyl]-3-benzylpiperidine-3-carboxylate hydrochloride was prepared according to similar manner as that of Example 9 as a white powder.

FT IR(KBr); 1726.0, 1673.9, 1631.5, 1604.5, 1581.3, 1546.6, 1517.7, 1490.7, 1454.1, 1444.4cm^{-1}

NMR(CD_3OD)(mixture of rotamers) δ; 1.05-5.30(31H, m), 6.80-7.30(9H, m).

(+)APCI MS m/z; 550(M^++1).

Anal: Calcd for $C_{32}H_{44}ClN_3O_5 \cdot 1\frac{3}{4}H_2O$: C, 62.22; H, 7.75; N, 6.80. Found: C, 62.27; H, 7.80; N, 6.67.

Example 24

N-[1-[(1-Methanesulfonylspiro[indoline-3, 4'-piperidine]-1'-yl)carbonyl]-2-(benzofuran-2-yl)ethyl] -2-tert-butoxycarbonylamino-2-methylpropanamide was prepared according to a similar manner to that of Example 8 as a foam.

FT IR(film); 1722, 1712, 1454, 1348, 1251, 1161cm^{-1}.

^{1}HNMR($CDCl_3$) δ; 1.38-2.00(19H, m), 2.60-3.30(7H, m), 3.60-3.90(2H, m), 4.00-4.20(1H, m), 4.45-4.65(1H, m), 4.89(1H, s), 5.30-5.50(1H, m), 6.10-7.60(9H, m).

(+)APCI MS m/z; 640(M^++1).

Example 25

N-[1-[(1-Methanesulfonylspiro[indoline-3, 4'-piperidine]-1'-yl)carbonyl]-2-(benzofuran-2-yl)ethyl]-2-amino-2-methylpropanamide hydrochloride was prepared according to a similar manner to that of Example 9 as a white powder.

FT IR(KBr); 1633, 1520, 1477, 1456, 1344, 1252, 1159cm^{-1}.

(+)APCI MS m/z; 539(M^++1).

^{1}HNMR(CD_3OD)(partial) δ; 1.40-2.00(10H, m), 2.70-3.00(5H, m), 3.80-4.30(3H, m), 4.40-4.60(1H, m), 5.30-5.50(1H, m), 6.30-7.70(9H, m).

Example 26

N-[1-[(1-Methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl)carbonyl]-2-(2,3-dihydrobenzofuran-2-yl)ethyl]-2-tert-butoxycarbonylamino-2-methylpropanamide was prepared according to a similar manner to that of Preration 24 as a foam.

^{1}HNMR($CDCl_3$) δ; 1.39-2.30(21H, m), 2.75-3.50(7H, m), 3.70-4.00(2H, m), 4.05-4.30 (1H, m), 4.50-5.45(4H, m), 6.70-7.42(8H, m). (+)APCI MS m/z; 641(M^++1).

Example 27

N-[1-[1-Methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl)carbonyl]-2-(2,3-dihydrobenzofuran-2-yl)ethyl]-2-amino-2-methyl-propanamide hydrochloride was prepared according to a similar manner to that of Example 9 as a white solid.

FT IR(KBr); 2931, 1678, 1630, 1529, 1456, 1344, 1240, 1157cm^{-1}.

^{1}HNMR(CD_3OD) δ; 1.60-2.31(12H, m), 2.80-3.05(5H, m), 3.10-3.50(2H, m), 3.80-4.70 (5H, m), 5.10-5.30(1H, m), 6.69-7.40(8H, m).

(+)APCI MS m/z; 541(M^++1).

Example 28

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride(301mg) was added to a solution of 1'-[2-amino-4-(2,3,4,5-tetrahydro-1-benzoxepin-5-yl) butanoyl]-1-methanesulfonylspiro[indoline-3,4'-piperidine](520mg), N-tert-butoxycarbonyl-α-methylalanine(238mg) and 1-hydroxybenzotriazole(165mg) in dichloromethane(20ml) at ambient temperature, and the resulting mixture was stirred at the same temperature overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with water and brine, dried over magunesium sulfate, and evaporated in vacuo. The residue was chromatographed (n-bexane-ethyl acetate) over silica gel, and active fractions were concentrated in vacuo to give a foam.

A suspension of this material in 4N-hydrogenchloride in ethyl acetate (5ml) was stirred at ambient temperature for 5 hours, and evaporated in vacuo. The residue was powdered from ethyl acetate and the powder was washed with diethyl ether to afford N-[1-[(1-methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl)carbonyl]-3-(2,3,4,5-tetrahydro-1-benzoxepin-5-yl)propyl]-2-amino-2-methylpropanamide

hydrochloride(466mg) as a white solid.
FT IR(KBr); 2933, 1631, 1522, 1481, 1346, 1232, 1159, 1047cm^{-1}.
^{1}HNMR(CD_3OD) δ ; 1.40-2.30(18H, m), 2.70-3.40(6H, m), 3.45-4.00(4H, m), 4.20-4.60 (2H, m), 4.65-4.80(1H, m), 6.85-7.40(8H, m).
(+)APCI MS m/z; 583(M^++1).

Example 29

N-[1-[(1-Methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl)carbonyl]-2-(chroman-3-yl)ethyl]-2-tert-butoxycarbonylamino-2-methylpropanamide was prepared according to a similar manner to that of Example 8 as a foam.
FT IR(film); 3394, 3388, 1720, 1712, 1641, 1491, 1456, 1348, 1250, 1161cm^{-1}.
^{1}HNMR($CDCl_3$) δ ; 1.42-1.61(5H, m), 1.69-1.91(6H, m), 2.20-2.28(1H, m), 2.46-3.25 (7H, m), 3.63-4.24(5H, m), 4.42-4.57(1H, m), 5.00-5.16(2H, m), 6.66-7.41(8H, m).
(+)APCI MS m/z; 655(M^++1).

Example 30

N-[1-[(1-Methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl)carbonyl]-2-(chroman-3-yl)ethyl]-2-amino-2-methylpropanamide hydrochloride was prepared according to a similar manner to that of Example 9 as a white solid.
FT IR(KBr); 2927, 1633, 1525, 1491, 1462, 1346, 1228, 1159, 1117cm^{-1}.
^{1}HNMR(CD_3OD) δ ; 1.57-2.10(12H, m), 2.80-3.24(7H, m), 3.84-4.22(5H, m), 4.40-4.48 (1H, m), 5.00-5.13(1H, m), 6.66-7.40(8H, m).
(+)APCI MS m/z; 555(M^++1).

Example 31

N-[[1-(2,3,4,5-tetrahydro-1-benzoxepin-4-yl)-2-oxo-2-(1-methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl)]ethyl]-2-tert-butoxycarbonylamino-2-methylpropanamide was prepared according to a similar manner to that of Example 8 as a foam.
FT IR(film); 2935, 1722, 1714, 1641, 1631, 1459, 1350, 1160cm^{-1}.
^{1}HNMR($CDCl_3$) δ ; 1.43(9H, s), 1.48(3H, d, J=3.2Hz), 1.55(3H, d, J=5.8Hz), 1.56-2.04(7H, m), 2.20-2.22(1H, m), 2.67-3.26(8H, m), 3.77-3.96(3H, m), 4.32-4.38(1H, m), 4.60-4.65(1H, m), 4.90-5.02(2H, m), 6.95-7.41(8H, m).

(+)APCI MS m/z; 679(M+1).

Example 32

N-[[1-(2,3,4,5-Tetrahydro -1-benzoxepin-4-yl)-2-oxo-2-(1-methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl)]ethyl-2-methylpropanamide hydrochloride was prepared according to a similar manner to that of Example 9 as a white powder.

^{1}HNMR(CD_3OD) δ; 1.49-2.31(13H, m), 2.71-3.54(7H, m), 3.74-4.58(5H, m), 4.92-5.02 (1H, m), 6.90-7.39(8H, m).

(+)APCI MS m/z; 592(M+1).

Example 33

1-Ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride(85mg) was added to a stirred mixture of 1'-[(2R)-2-amino-3-(2,3,4,5-tetrahydro-1-benzoxepin-4-yl)propianyl]-1-methanesulfonylspiro-[indoline-3,4'-piperidine](74.2mg), 1-tert-butoxycarbonylazetidine-4-carboxylic acid(74.2mg), and 1-hydroxybenzotriazole(46.8mg) in dichloromethane(20mg). After stirring for 4 hours, the reaction mixture was evaporated, and the residue was partitioned between ethyl acetate and water. The organic layer was separated, washed in turn with 0.1N aqueous hydrochloric acid, brine, a saturated solution of sodium hydrogen carbonate in water and brine(twice), and dried over magnesium sulfate. Evaporation of the solvent gave a residue, which was chromatographed on silica gel eluting with a mixture of n-hexane and ethyl acetate. Active fractions were combined and concentrated in vacuo to give a foam.

A solution of this material in 4N hydrogenechloride ethyl acetate(5ml) was stirred for 4 hours at ambient temperature. The reaction mixture was evaporated and azeotroped three times with ethyl acetate to give a powder. The powder was collected, washed with ethyl ether, and dried in vacuo to give azetidine-3-carboxylic acid[1-[(2,3,4,5-tetrahydro-1-benzoxepin-4-yl)methyl]-2-oxo-2-(1-methanesulfonylspiro[indoline-3,4'-piperidine])-1'-yl]ethylamide hydrochloride (128mg) as a white solid.

^{1}HNMR(CD_3OD)(partial) δ; 1.50-2.20(9H, m), 2.60-3.05(6H, m), 3.60-4.65(10H, m), 4.90-5.15(1H, m), 6.85-7.45(8H, m).

(+)APCI MS m/z ; 567(M+1).

Example 34

1-Ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride(85mg) was added to a stirred mixture of 1'-[(2R)-2-amino-3-(2,3,4,5-tetrahydro-1-benzoxepin-4-yl)propionyl]-1-methanesulfonylspiro-[indoline-3,4'-piperidine](140mg), 1-tert-butoxycarbonyl-4-isonipecotic acid(65.9mg) and 1-hydroxybenzotriazole(46.9mg) in dichloromethane(10ml). After stirring for 4 hours, the reaction mixture was evaporated and the residue was partitioned between ethyl acetate and water. The organic layer was separated, washed in turn with 0.1N aqueous hydrochloric acid, brine, a saturated solution of sodium hydrogen carbonate in water and brine (twice), and dried over magnesium sulfate. Evaporation of the solvent gave a residue, which was chromatographed on silica gel eluting with a mixture of n-hexane and ethyl acetate. Active fractions were combined and concentrated in vacuo to give a foam.

A solution of this material in 4N hydrogenechloride in ethylacetate (5ml) was stirred for 2 hours at ambient temperature. The reaction mixture was evaporated and azeotroped three times with ehytl ether, and dried in vacuo to give piperidine-4-carboxylic acid [1-[(2,3,4,5-tetrahydro-1-benzoxepin-4-yl)-methyl]-2-oxo-2-(1-methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl)]ethyl amide hydrochloride(100mg) as a white sloid.

(+)APCI MS m/s;595(M+1).

Example 35

N-[1-[(1-Methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl)carbonyl]-2-((R)-2,3,4,5-tetrahydro-1-benzoxepin-4-yl)ethyl]-2-[(tert-butoxycarbonyl)amino]-2-methylpropanamide was prepared in a similar manner to that of Example 9.

A colorless powder; mp75℃(dec.).

IR(Nujol); 3370, 3280, 1700, 1625, 1340, 1150cm^{-1}.

^{1}HNMR($CDCl_3$) δ ; 1.20-2.30(24H, m), 2.60-3.30(4H, m), 2.92(3H, s), 3.55-4.35(5H, m) 4.58(1H, m), 4.85 and 4.90(1H, each s), 5.06(1H, m), 6.93-7.30(8H, m), 7.40(1H, d, J=7.9Hz).

(+)APCI MS m/z; 669(M+1), 569(M-Boc+2).

Example 36

2-Amino-N-[1-[(1-methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl) carnbonyl]-2-((R)-2,3,4,5-tetrahydro-1-benzoxepin-4-yl)ethyl]-2-methylpropanamide hydrochloride was prepared in a similar manner to that of Example 10.

A colorless powder; mp169℃(dec.).

IR(Nujol); 3400-3100, 2750-2550, 1665, 1620, 1340, 1155cm^{-1}.

^{1}HNMR(CD_3OD) δ; 1.56-2.15(15H, m), 2.65-3.40(4H, m), 2.97(3H, s), 3.65-4.35(5H, m), 4.49(1H, m), 5.03(1H, m), 6.87-7.29(7H, m), 7.38(1H, d, J=7.9Hz).

(+)APCI MS m/z; 569(M$^+$+1).

Anal. Calcd for $C_{30}H_{40}N_4O_5S \cdot HCl \cdot 1.2H_2O$: C, 57.49; H, 6.98; N, 8.94. Found: C, 57.45; H, 7.03; N, 8.51.

Example 37

Ethyl 3-benzyl-1-[2-(2-tert-butoxycarbonylamino-2-methylpropionylamino)-3-(2,3-dihydro-1-benzoxepin-4-yl)propionyl]piperidine-3-carboxylate was prepared in a similar manner to thet of Example 1.

A colorless powder(washed with n-hexane).

IR(Nujol); 3400, 3310, 1725, 1705, 1670, 1635, 1615cm^{-1}.

^{1}HNMR($CDCl_3$) δ; 1.05-1.80(22H, m), 2.00-3.70(8H, m), 3.90-5.30(8H, m), 6.05-6.20 (1H, m), 6.80-7.30(9H, m).

(+)APCI MS m/z; 648(M$^+$+1).

Example 38

Ethyl 1-[2-(2-tert-butoxycarbonylamino-2-methylpropionylamino)-3-(2,3-dihydro-1-benzoxepin-4-yl)propionyl]-3-benzylpiperidine-3-carboxylate was prepared in a similar manner to that of Example 9.

A pale green powder(powdered from diethyl ether-n-hexane); mp109℃(dec.).

IR(Nujol); 3360(br), 2750-2550, 1720, 1670, 1625cm^{-1}.

(+)APCI MS m/z; 548(M$^+$+1).

Example 39

N-[(1R)-1-[1-Methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl)

carbonyl]-2-(2,3,4,5-tetrahydro-1-benzoxepin-4-yl)ethyl]-1-amino-1-cyclopropane-carboxamide hydrochloride was prepared according to a similar manner to that of Example 28.

^{1}HNMR(CD_3OD) δ ; 1.25-2.20(13H, m), 2.65-3.45(7H, m), 3.60-4.60(6H, m), 5.00-5.20 (1H, m), 6.85-7.45(8H, m).

(+)APCI MS m/z; 567(M^++1).

Example 40

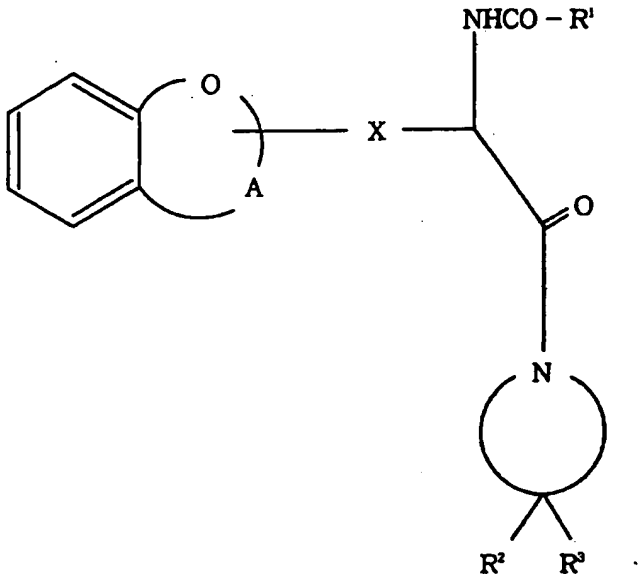
N-[(1R)-1-[(1-Methanesulfonylspiro[indoline-3,4'-piperidine]-1'-yl) carbonyl]-2-(2,3,4,5-tetrahydro-1-benzoxepin-4-yl)ethyl]-1-amino-1-cyclopentane carboxamide hydrochloride was prepared according to a similar manner to that of Example 28.

^{1}HNMR(CD_3OD) δ ; 1.55-2.50(17H, m), 2.60-3.45(7H, m), 3.55-4.60(6H, m), 4.95-5.15 (1H, m), 6.85-7.45(8H, m).

(+)APCI MS m/z; 595(M^++1).

CLAIMS

1. A compound of the formula:



wherein R^1 is 3-azetidinyl, 4-piperidyl or

a group of the formula:

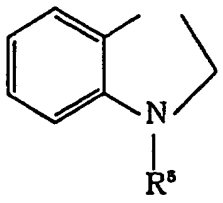
-Y-NHR⁴

in which R^4 is hydrogen or amino protective group, and Y is lower alkylene or cyclo(lower) alkylene,

R^2 is cyano and R^3 is aryl;

R^2 is esterified carboxy and R^3 is ar(lower)alkyl: or

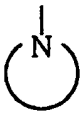
R^2 and R^3 are linked together to form



in which R^5 is acyl,

A is $-(CH_2)_n-$, in which n is 2, 3 or 4, vinylene or butenylene,

X is bond or lower alkylene, and

 is piperidino,

and pharmaceutically acceptable salts thereof.

2. The compound of claim 1, wherein

R^1 is 3-azetidinyl, 4-piperidyl or

a group of the formula:

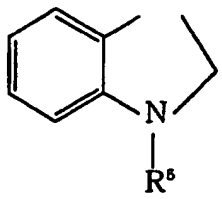
$-Y-NHR^4$

in which R^4 is hydrogen or lower alkoxycarbonyl, and Y is lower alkylene or cyclo(lower) alkylene,

R^2 is cyano and R^3 is phenyl;

R^2 is lower alkoxycarbonyl and R^3 is benzyl: or

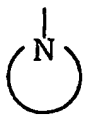
R^2 and R^3 are linked together to form



in which R^5 is lower alkanesulfonyl,

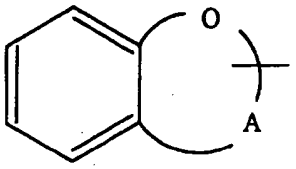
A is $-(CH_2)_n-$, in which n is 2, 3 or 4, vinylene or butenylene,

X is bond or lower alkylene, and

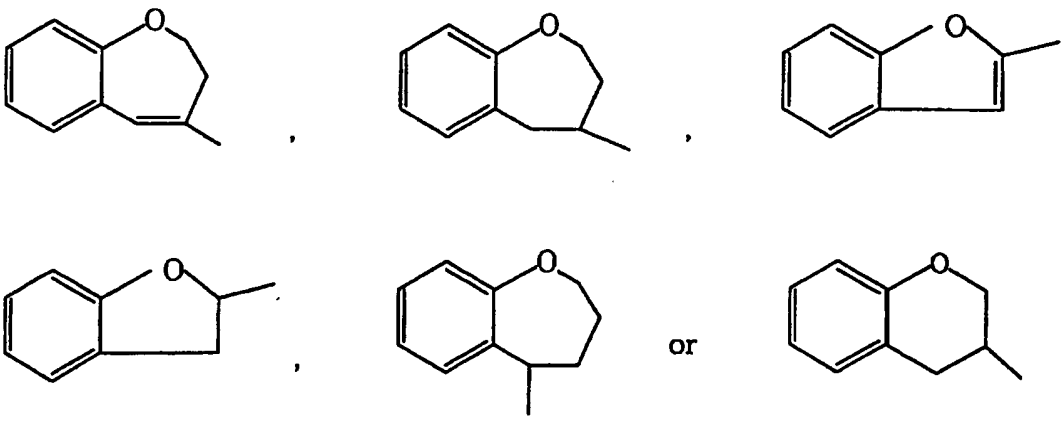


is piperidino.

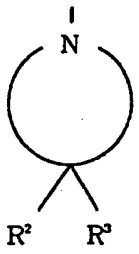
3. The compound of claim 2, wherein



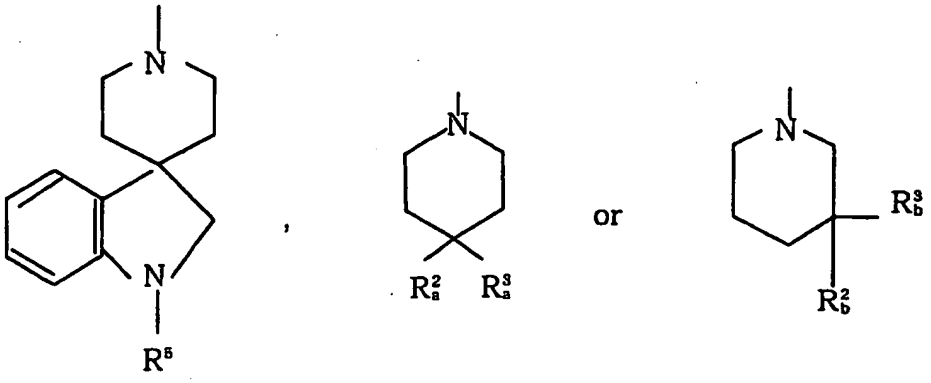
is the following formula :



4. The compound of claim 3, wherein



is the following formula :



in which R^5 is lower alkanesulfonyl,

R^2_a is cyano,

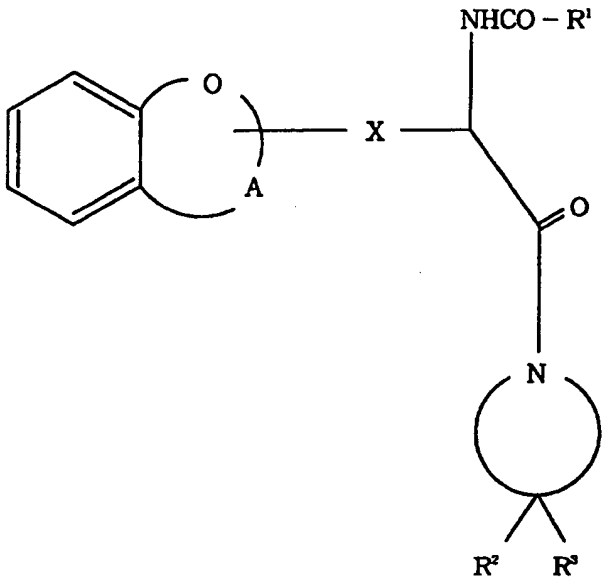
R^2_b is lower alkoxycarbonyl,

R^3_a is phenyl, and

R^3_b is benzyl.

5. A process for preparing

a compound of the formula :



wherein R^1 is 3-azetidinyl, 4-piperidyl or

a group of the formula:

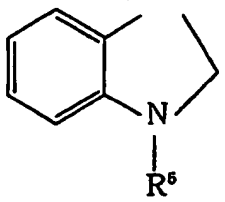
$$-Y-NHR^4$$

in which R^4 is hydrogen or amino protective group, and Y is lower alkylene or cyclo(lower) alkylene,

R^2 is cyano and R^3 is aryl;

R^2 is esterified carboxy and R^3 is ar(lower)alkyl: or

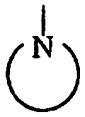
R^2 and R^3 are linked together to form



in which R^5 is acyl,

A is $-(CH_2)_n-$, in which n is 2, 3 or 4, vinylene or butenylene,

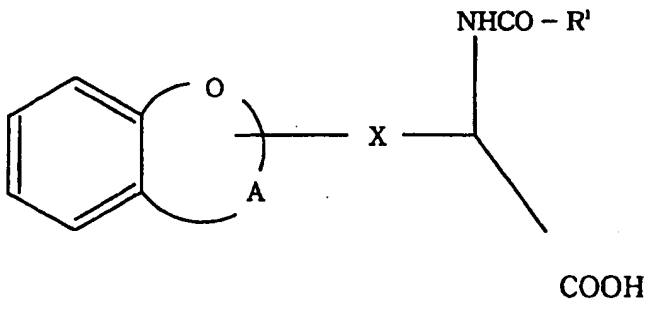
X is bond or lower alkylene, and

 is piperidino,

or pharmaceutically acceptable salts thereof,

which comprises,

(1) reacting a compound of the formula :



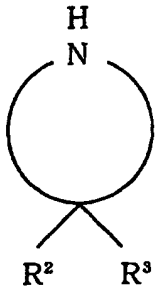
wherein R^1, A and X are each as defined above,

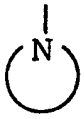
or its reactive derivative

at the carboxy group

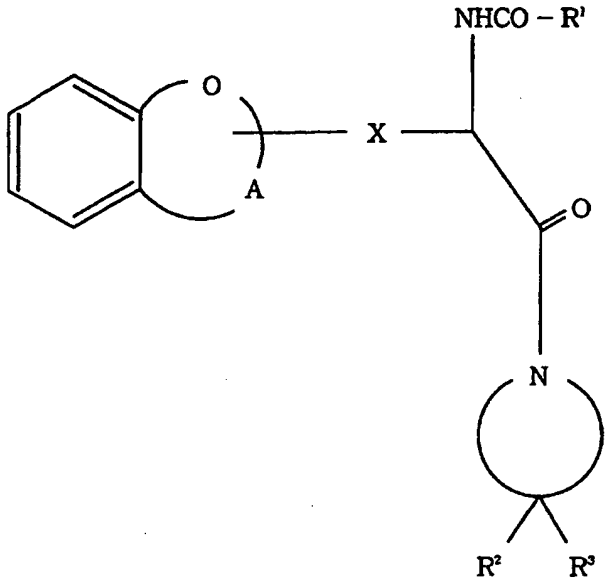
or a salt threof,

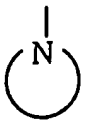
with a compound of the formula :



wherein R^2, R^3 and  are each as defined above,

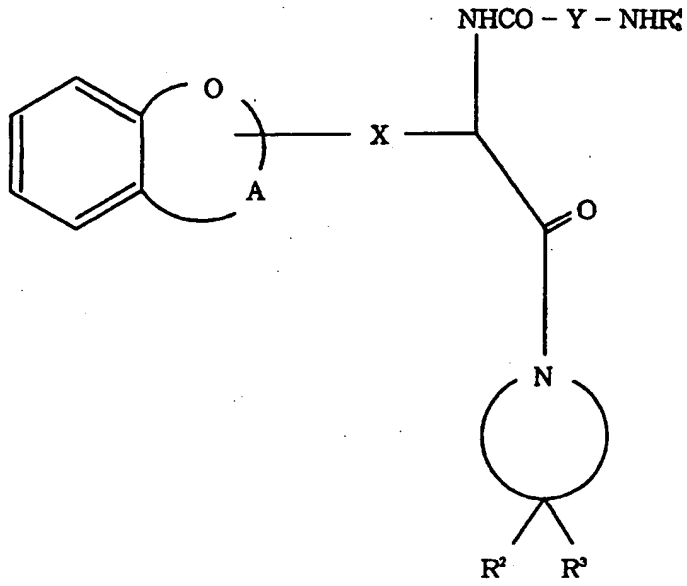
or its reactive derivative at the amino group or a salt thereof, to give a compound of the foumula:

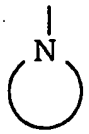


wherein R^1, R^2, R^3, A, X and  are each as defined above,

or a salt thereof , or

(2) subjecting a compound of the foromula :



wherein R^2, R^3, A, X, Y and  are each as defined above ,

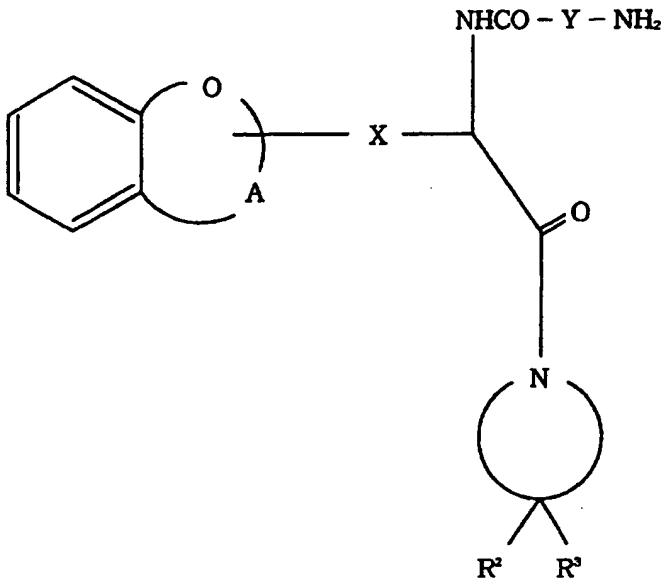
and

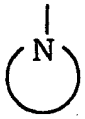
R_a^4 is amino protective group,

or a salt thereof,

to removal reaction of amino protective group,

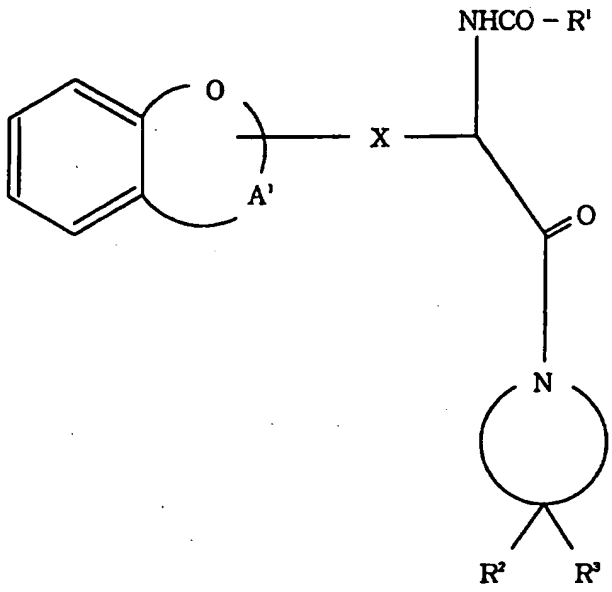
to give a compownd of the formula :



wherein R^2, R^3, A, X, Y and  are each as defined above,

or a salt thereof, or

(3) subjecting a compound of the formula:

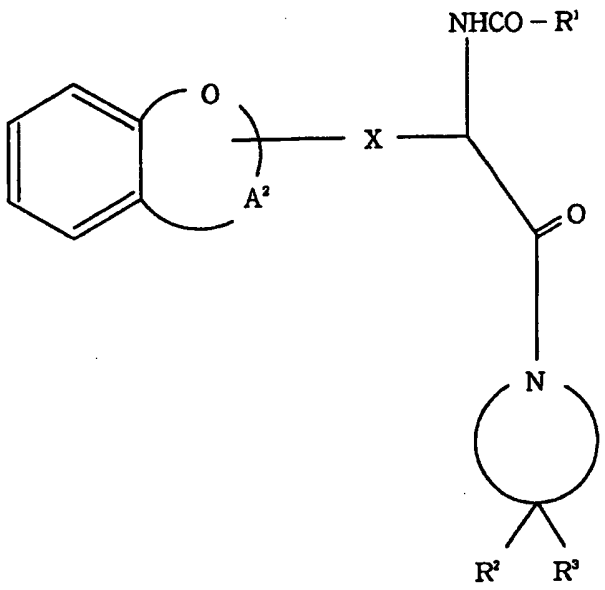


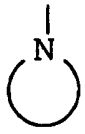
wherein R^1, R^2, R^3, X and  are each as defined above, and

A^1 is vinylene or butenylene,,

or a salt thereof, to reduction reaction,

to give a compound of the formula:

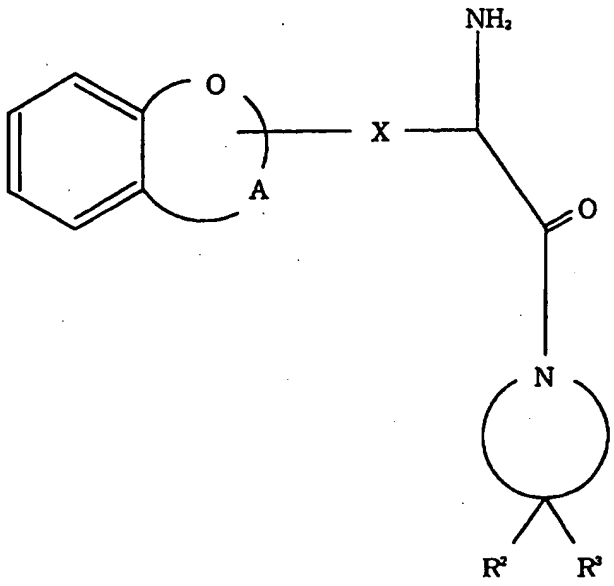


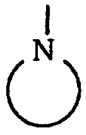
wherein R^1 R^2, R^3, X and  are each as defined above, and

A^2 is ethylene or tetramethylene,

or a salt thereof, or

(4) reacting a compound of the formula :

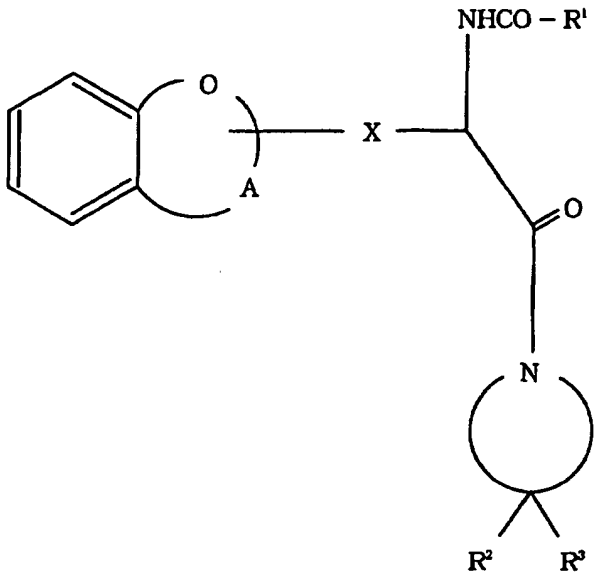


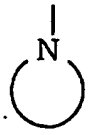
wherein R^2, R^3, A, X, and  are each as defined above,

or its reactive derivatives at the amino group,
or a salt thereof, with a compound of the formula:

R^1-COOH

wherein R^1 is as defined above,
or its reactive derivatives at the carboxy group,
or a salt thereof,
to give a compowund of the formula :



wherein R^1, R^2, R^3, A, X, and  are each as defined above,

or a salt thereof.

6. A pharmaceutical composition, which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers.

7. A method for the treatment of obesity in combination with an $\alpha 2$ or $\beta 3$ adrenergic agonist, osteoporosis in combination with parathyroid hormone, the catabolic effects of nitrogen wasting in combination with insulin-like growth factor 1, growth retardation, renal failure or insufficiency, schizophrenia, sleep disorder, skeletal dysplasia, depression, Alzheimer's disease, pulmonary dysfunction, hyperinsulinemia, ulcer, arthritis, cardiac dysfunction, replacement for elderly people, ALS, growth hormone deficient adults, physiological short stature including growth hormone deficient children , Turner's syndrome, intrauterine growth refardation, cachexia and protein loss due to cancer or AIDS, which comprises administering a compound of claim 1 or a pharmaceutically acceptable salt thereof to human or animals.

8. A use of a compound of claim 1 as a medicament.

9. A use of a compound of claem 1 or a pharmaceutically acceptable salt thereof as a promoter of growth hormone release.

INTERNATIONAL SEARCH REPORT

Intern nal Application No
PC 97/03704

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D471/10 A61K31/445 C07D405/06 C07D405/14 C07K5/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 97 11697 A (MERCK & CO INC ;YANG LIHU (US); MARQUIS ROBERT W (US); OLSON JOHN) 3 April 1997 see page 8, line 16; claim 1 ---	1-9
Y	EP 0 662 481 A (MERCK & CO INC) 12 July 1995 cited in the application see page 7, line 17; claim 1 ---	1-9
Y	EP 0 615 977 A (MERCK & CO INC) 21 September 1994 cited in the application see page 6, line 15; claim 1 ---	1-9
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

3

Date of the actual completion of the international search	Date of mailing of the international search report
9 January 1998	30. 01. 98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gettins, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern[illegible]nal Application No
PC[illegible] 97/03704

C.(Continuation) DOCUMENTS CONS[illegible]RED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 13265 A (MERCK & CO INC ;NARGUND RAVI (US); PATCHETT ARTHUR A (US); YANG LI) 9 May 1996 see page 3, line 12 - line 14 -----	1-9

3

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 97/03704

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 7
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 97/03704

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9711697 A	03-04-97	AU 7169696 A	17-04-97
EP 0662481 A	12-07-95	US 5578593 A	26-11-96
		AU 673017 B	24-10-96
		AU 5232193 A	23-06-94
		CA 2110672 A	12-06-94
		CN 1092767 A	28-09-94
		HR 931484 A	30-04-96
		JP 2509147 B	19-06-96
		JP 7097367 A	11-04-95
		MX 9307851 A	30-06-94
		SI 9300647 A	30-09-94
		AU 673552 B	14-11-96
		AU 5232093 A	23-06-94
		BG 99710 A	31-01-96
		CA 2110670 A	12-06-94
		CN 1092071 A	14-09-94
		CZ 9501514 A	13-12-95
		CZ 9501515 A	13-12-95
		EP 0615977 A	21-09-94
		FI 952862 A	09-06-95
		FI 952863 A	09-06-95
		HU 9500324 A	28-09-95
		HU 73228 A	29-07-96
		HU 72076 A	28-03-96
		JP 2509530 B	19-06-96
		JP 6263737 A	20-09-94
		MX 9307850 A	30-06-94
		NO 952294 A	10-08-95
		NO 952295 A	10-08-95
		NZ 258412 A	29-01-97
		NZ 258429 A	26-05-97
		PL 309331 A	02-10-95
		PL 309332 A	02-10-95
		SI 9300646 A	30-09-94
		SK 75995 A	08-11-95
		WO 9413696 A	23-06-94
		WO 9419367 A	01-09-94
		US 5536716 A	16-07-96
		US 5652235 A	29-07-97

INTERNATIONAL SEARCH REPORT

[redacted]tion on patent family members

Intern. nal Application No
PCT/[redacted]97/03704

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0662481 A		ZA 9309272 A	08-08-94
		ZA 9309274 A	08-08-94
EP 0615977 A	21-09-94	US 5536716 A	16-07-96
		AU 673552 B	14-11-96
		AU 5232093 A	23-06-94
		BG 99710 A	31-01-96
		CA 2110670 A	12-06-94
		CN 1092071 A	14-09-94
		CZ 9501514 A	13-12-95
		FI 952863 A	09-06-95
		HU 9500324 A	28-09-95
		HU 72076 A	28-03-96
		JP 2509530 B	19-06-96
		JP 6263737 A	20-09-94
		MX 9307850 A	30-06-94
		NO 952295 A	10-08-95
		NZ 258412 A	29-01-97
		PL 309331 A	02-10-95
		SI 9300646 A	30-09-94
		SK 75995 A	08-11-95
		WO 9413696 A	23-06-94
		US 5652235 A	29-07-97
		AU 673017 B	24-10-96
		AU 5232193 A	23-06-94
		CA 2110672 A	12-06-94
		CN 1092767 A	28-09-94
		CZ 9501515 A	13-12-95
		EP 0662481 A	12-07-95
		FI 952862 A	09-06-95
		HR 931484 A	30-04-96
		HU 73228 A	29-07-96
		JP 2509147 B	19-06-96
		JP 7097367 A	11-04-95
		MX 9307851 A	30-06-94
		NO 952294 A	10-08-95
		NZ 258429 A	26-05-97
		PL 309332 A	02-10-95
		SI 9300647 A	30-09-94
		WO 9419367 A	01-09-94

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. nal Application No
PC[redacted] 97/03704

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0615977 A		US 5578593 A	26-11-96
		ZA 9309272 A	08-08-94
		ZA 9309274 A	08-08-94
WO 9613265 A	09-05-96	AU 3964795 A	23-05-96
		CA 2202784 A	09-05-96
		EP 0785784 A	30-07-97